

MAR 21 1931

VOLUME 31

NUMBER 3

# ARCHIVES OF PATHOLOGY

## EDITORIAL BOARD

LUDWIG B. GROSS, Chicago

NEWING, New York

WILLIAM OSER, San Francisco

SOLBACK, Boston

W. C. MACCALLUM, Rochester

STENGEL, Philadelphia

OSCAR T. SCHUBERT, Rochester, N.Y.

MARCH, 1931

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH  
DEARBORN STREET, CHICAGO, ILL. ANNUAL SUBSCRIPTION, \$3.00

Entered as Second-Class Matter, Jan. 24, 1910, under Postoffice of Chicago, Illinois, Under the Act of Oct. 3, 1917, authorized for mailing at special rate of postage provided for in the Act of Feb. 26, 1949, authorized Jan. 27, 1950.

# CONTENTS OF PART NUMBER

FEBRUARY, 1911. NUMBER 2

The Effect of Ultraviolet Light. E. R. Peck, M.D., Philadelphia, Pa.

Experimental Tubercle Infection in Dogs and in Rabbits. V. E. Hunt, M.D., and H. L. Hunt, M.D., Philadelphia.

Chronic Pharyngitis (Chronic Throat) in Children. Report of a Case. W. J. Hunt, M.D., and John H. Hunt, M.D., Philadelphia.

Chronic Pharyngitis Taken by Operation. Report of a Case. W. J. Hunt, M.D., and John H. Hunt, M.D., Philadelphia.

Chronic Pharyngitis of the Larynx. Report of a Case. Joseph H. Hunt, M.D., Philadelphia.

Effect of Blood Platelets to Edematous Tissue. Light, Iodine and Carbon. R. Steiner, M.S., and H. L. Hunt, M.D., Chicago.

Effect of Invasion of Blood Vessels of the Thyroid Gland. H. L. Hunt, M.D., Boston.

Syphilis: Its Frequency, Pathogenesis, and Appearance. H. L. Hunt, M.D., Kalamazoo, Mich.

Current Literature.

Conclusions: Biological Society.

# ARCHIVES OF PATHOLOGY

VOLUME 11

MARCH, 1931

NUMBER 3

## THE BLOOD PROTEINS

WITH SPECIAL REFERENCE TO THE CHANGES OCCURRING  
IN RENAL DISEASES \*

ALBERT E. KUMPF, M.D.

MINNEAPOLIS

The purpose in this work has been to make a study of the changes in the proteins of serum and plasma especially in renal diseases, but also in some other conditions.

### TECHNIC

In the earlier analyses, the proteins were determined with the refractometer, and according to the technic of Robertson. But since it was suspected that the values as determined by this method were too high in the case of lipemic, milky serums, other methods were employed. The nonprotein nitrogen was determined by the method of Folin and Wu; the fibrinogen and total globulins were precipitated according to the method of Howe, and total and albumin nitrogen determined by the micro-Kjeldahl technic of Berglund.

### THE PROTEINS OF NORMAL SERUM AND PLASMA

*Observations Recorded in the Literature.*—In a normal person, the protein content of the serum is subject to considerable variation. A slight increase has been observed after a cold bath (von Farkas) and after muscular exercise (Reisz; Böhme). Pressure, congestion (Böhme) and stasis resulting from the application of a tourniquet cause a marked rise in the protein concentration. Reisz found that in venous congestion the refractive index of the serum increased from 59.03 to 74.69; while in stasis (tourniquet) there might be an increase in serum protein of as much as 0.4 Gm. per hundred cubic centimeters. The same has been found after the removal of large amounts of pleural or peritoneal fluid (Barlocci). An increased carbon dioxide content of blood likewise produces a transient rise in the serum proteins, which, however, at once returns to normal if the acidity is increased (Böhme).

There is a fairly constant drop in the serum protein concentration following severe hemorrhage and menstruation (Reisz; Oliva).

Changes in body temperature and perspiration have an inconstant effect. According to Sandelowsky and Böhme, the blood becomes more

\* Submitted for publication, Sept. 16, 1930.

\* From the Department of Pathology of the University of Minnesota.

concentrated. Reisz at times found just the opposite. A seasonal variation is also possible (Reisz).

Drinking pure water produces no appreciable change in the serum concentration of normal individuals (Engel; Scharl). The administration of large quantities of sodium chloride caused a transient thickening of the serum, even in the presence of a slight disturbance of the normal water balance (Benzür). Reisz, on the contrary, found a transitory thinning.

In a normal person, an average diet produces no constant or appreciable change in the concentration of the serum protein (Reisz; Tranter and Rowe; Kahn; Böhme). The effect of starvation is open to question. Reisz stated that there is an increased concentration of the serum proteins, due to dehydration. Geill, in a review of the literature to 1927, was unable to find either an increase or a decrease reported.

The differences in serum proteins as between males and females are, at most, small and insignificant. Tranter and Rowe found a slightly higher globulin in females, while Lewinski was able to find this only in pregnancy. Geill and Salvesen concluded that the differences are negligible. The total serum protein is low in new-born infants, but increases rapidly with age, so that adult values are reached at the age of about 1½ years or soon thereafter (Reisz; Stahlberg; J. Munk; Geill).

It has been found, however, that, if the variations mentioned are guarded against, the concentration of the serum protein of a given individual is remarkably constant from day to day (Böhme; Muschel).

Much depends on the technic used, and values for the serum proteins must be interpreted accordingly, both in the normal and in the pathologic case. The older analysis, for the most part, consisted in precipitating the total serum protein with some salt, such as ammonium or magnesium sulphate, drying and weighing. Frequently the precipitated protein was unpurified; yet this is an important step. Reisz pointed out that the values for total protein found by this direct method were considerably higher than those secured by the Kjeldahl method, unless the precipitates were purified. The results were then much more uniform. Limbeck and Pick, in making a similar comparison, found that the results varied all the way from 0.8 to 21.5 Gm. per hundred cubic centimeters.

The serum protein values determined by the refractometric method have been found to be a little higher than those calculated from the Kjeldahl method (Reisz; Linder, Lundsgaard and Van Slyke). The refractometer readings are, no doubt, much too high in the case of lipemic serums (Epstein). Rowe, using Robertson's technic, found a fair agreement between his results and those secured by the Kjeldahl method. He pointed out that, as previously shown by Schorer, since there are marked variations in the albumin-globulin ratio in various

diseases, and since these fractions have different refractive indexes, the figures for total serum protein calculated according to the method and tables of Reisz are frequently erroneous. Reisz stated that the difference between his method and the direct method was only about

TABLE 1.—*The Proteins of Normal Serum and Plasma (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	Fibrin, per Cent
Berzelius,* 1831	8.0	.....	.....	.....
Marcett,* 1831	8.7	.....	.....	.....
Denle,* 1838	8.0	.....	.....	.....
Lecanu,* 1837	7.8 to 8.1	.....	.....	.....
Bostok,* 1842	10.0	.....	.....	.....
Nasse,* 1836	7.2 to 9	.....	.....	.....
Becquerel and Rodier,* 1845	8	.....	.....	.....
Otto,* 1848	7.5 to 8	.....	.....	.....
C. Schmidt,* 1850	7.4 to 8.3	.....	.....	.....
Leven,* 1873	7.9	.....	.....	.....
Hammarsten, 1878	7 to 8.1	3.85 to 5.3	2.48 to 3.74	.....
Hoffman, 1882	7.36 to 7.76	5.04 to 5.28	2.08 to 2.72	.....
Mya-Viglezio, 1888	8.15	5.72	2.43	.....
Limbeck and Plek, 1898	6.5 to 7.4	3.82 to 3.83	1.58 to 1.97	.....
von Jaksch, 1898	8.44 to 9.19	.....	.....	.....
Lewinski, 1908	6.7 to 7.6	.....	.....	.....
Erben, 1905	8.5	3.85 to 5.38	2.48 to 3.78	.....
Reisz, 1902; 1912	7 to 9	.....	.....	.....
Strauss and Chajes	7 to 8.7	.....	.....	.....
Engel	7.4 to 9.4	.....	.....	.....
Martius	7.0 to 9.3	.....	.....	.....
Goldammer	6.6 to 9.1	.....	.....	.....
Böhme	6.8 to 8.9	.....	.....	.....
Widal, Bernard and Vaucher	7.6 to 8.4	.....	.....	.....
Winternitz, 1908	5.11 to 5.68	3.92 to 4.01	1.19 to 1.67	0.17 to 0.24
Winternitz, 1910	7.8 to 8.40	.....	.....	0.46
Epstein, 1912	8.3	5.09	3.07	.....
Epstein, 1913	6.48 to 8.1	2.53 to 5.1	2.1 to 3.2	.....
Tranter and Rowe, 1915	6.7 to 8.7	4.95 to 7.7	1 to 2.54	.....
Rowe, 1916	6.5 to 8.2	4.6 to 6.7	1.2 to 2.3	.....
Epstein, 1917	7.4	4.66	2.73	.....
Loeper and Tonnet, 1918	7.8 to 8.0	.....	.....	.....
Dienat, 1918	7.17	.....	.....	.....
Zangemeister, 1919	7.78	.....	.....	.....
Kahn, 1920	6.76 to 8.47	4.39 to 5.43	2.25 to 3.21	.....
Epstein, 1922	6.0 to 8.0	.....	.....	.....
Rusznýk, Barát and Kürthy, 1924	.....	3.25 to 4.39	1.25 to 2.07	0.12 to 0.24
Schindera, 1924	.....	4.2 to 6.8	1.3 to 3.5	0.1 to 0.26
Linder, Lundsgaard and van Slyke, 1924	6.22 to 7.45	3.36 to 4.0	2.36 to 2.89	.....
Fahr and Swanson, 1926	7.2	4.9	2.3	0.3
Myers, 1924	6.5 to 8.2	4.6 to 6.7	1.2 to 2.3	.....
Lewin, 1927	.....	.....	.....	.....
Salvesen, 1927	6.53 to 7.96	3.95 to 5.24	1.96 to 3.16	.....
Kollert and Starlinger, 1922	7.0 to 9.0	.....	.....	0.13 to 0.3
Stahlberg, 1928	7.8 to 8.1	.....	.....	.....
Kapteyn, 1928	.....	.....	.....	.....
Lloyd and Paul, 1928	.....	.....	.....	.....
Starlinger and Winands, 1928	6.93 to 9.13	4.21 to 5.78	1.41 to 4.03	0.36
von Parkas, 1928	6.1 to 8.7	3.6 to 5.5	1.4 to 3.9	0.2 to 0.3
Jones, 1929	5.86 to 8.42	4.12 to 6.1	1.05 to 2.96	0.18 to 0.3
Munk, 1929	6.9 to 7.8	4.4 to 5	2.1 to 2.8	.....
Winternitz, 1909	.....	.....	.....	0.39 to 0.6
Pfeiffer, 1897	.....	.....	.....	0.31 to 0.75
Lester, 1923	.....	.....	.....	0.25 to 0.4
Gram, 1923	.....	.....	.....	0.38, 0.2 to 2
Foster, 1924	.....	.....	.....	0.33 ± 5

\* Quoted by Rowe.

±0.23 per cent. Chiray and Demanche, however, stated that the results secured by these two methods differed all the way from 1 to 17 per cent. In a later paper, Reisz admitted Schorer's corrections. Sources of error due to changes in the albumin-globulin ratio are, however, greatly reduced by Robertson's technic. A comparison of his results with

results secured by the direct method showed a variation of  $\pm 0.2$  per cent in the albumin value and of  $\pm 0.15$  per cent in the globulin value.

Table 1, which embodies all the available data on the protein contents of normal serum, demonstrates that the values for total protein obtained by different investigators are fairly uniform. The albumin and globulin values, on the contrary, show marked variations, no doubt dependent on the different salts used in the salting out process. The same variation was found by Geill in his review (1927).

*Personal Observations.*—The results of a series of combined analyses on the serums of eight normal males are given in table 2. Blood was taken from one of the veins in the antecubital fossa. With one exception (F. H. case 5), none of the subjects had taken food for at least twelve hours. The blood was allowed to clot and the serum was used at once for analysis.

TABLE 2.—*The Proteins of Normal Serum (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Non-protein Constituents	Non-protein Nitrogen
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl		
1	7.78	7.51	4.86	4.30	2.92	3.31	1.66	1.27	1.42	37.5
2	7.46	6.65	5.81	4.89	1.65	1.76	3.50	2.70	1.52	30.5
3	7.37	6.91	5.45	5.18	1.92	1.73	2.84	2.90	1.72	35.7
4	7.06	....	4.74	....	2.31	....	2.00	....	1.43	....
5	7.33	7.54	4.83	4.68	2.50	2.86	1.93	1.60	1.80	42.9*
6	7.13	7.25	5.10	4.88	2.03	2.37	2.50	2.06	1.50	30.5
7	7.58	7.27	5.93	5.44	1.65	1.83	3.50	2.97	1.40	27.6
8	7.18	7.04	4.80	4.49	2.29	2.55	2.14	1.76	1.60	27.3
Max.	7.78	7.54	5.93	5.44	2.92	3.31	3.50	2.90	1.80	42.9*
Min.	7.06	6.65	4.86	4.20	1.65	1.73	1.66	1.27	1.40	27.3
Aver.	7.36	7.17	5.20	4.82	2.16	2.34	2.52	2.19	1.51	33.1

\* After a meal.

The total protein values as determined by the two methods were rather uniform. In six of the eight cases, the refractometric value exceeded that found by the Kjeldahl method. The differences range from  $-0.12$  to  $+0.81$  Gm. per hundred cubic centimeters. The greatest variations were found in the albumin-globulin ratios. The maximum difference here was 0.83 per cent. The average value of the non-protein constituents of the blood was also a little higher than that found by Tranter and Rowe (1.5 as compared with 1.1 and 1.3 of Tranter and Rowe).

#### THE PROTEINS OF SERUM AND PLASMA IN RENAL DISEASES

*Observations in the Literature.*—The reported cases of changes in serum and plasma proteins in renal diseases have been arranged in five groups, and the results are given in tables 3 to 5. The grouping is

often uncertain, since many authors use the old terminology; but it is the best that can be done with the available data.

Group 1, Acute and Subacute Glomerulonephritis (table 3): The results in this group were fairly uniform. Seven of the ten investigators reported a moderate reduction of albumin and of total protein with normal or slightly increased globulin. The albumin-globulin ratio was lowered and at times reversed. In many cases there appeared to be a correlation between the amount of edema and the lowering of the total serum protein. This was, however, by no means constant. Similar observations were reported by Geill in his review (1927).

TABLE 3.—*The Proteins of Serum and Plasma in Acute and Subacute Glomerulonephritis (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Nonprotein Constituents	Fibrin, per Cent
Erben, 1905	Slight reduction	.....	.....	.....	.....	.....
Reisz, 1913	Reduced $\pm$	.....	.....	.....	.....	.....
Rowe, 1916	5.2 to 7.0	3.1 to 3.6	2.1 to 3.4	.....	1.5 to 1.6	.....
Kahn, 1920	5.86 to 7.96	3.62 to 4.37	2.24 to 3.8	.....	Normal	.....
Weltmann and Neumayer, 1925	.....	.....	.....	.....	.....	Increased
Fahr and Swanson, 1926	4.1 to 8.4	1.6 to 5.2	1.6 to 3.6	0.45 to 2	.....	0.3 to 1.3
Kollert and Starlinger, 1922	.....	.....	Normal	.....	.....	Increased
Miller, McIntosh and van Slyke, 1927	.....	1.38 to 2.06	2.55 to 2.82	0.51 to 1.06	.....	.....
Schwartz and Kohn, 1922	4.2 to 7.15	.....	.....	.....	.....	.....
J. Munk, 1929	Variable	Reduced	Increased	Reversed	.....	.....

Erben and Reisz found a normal, or at most, a slightly reduced total protein, and Kahn was unable to show any appreciable variation in the albumin, globulin or total protein values. In some of J. Munk's cases there were total protein values of 9 per cent or more. Reisz, however, pointed out that there was a slight reduction in serum protein in cases that showed edema. A consistent increase in fibrinogen has been reported but the number of analyses is too small to be of much value.

Group 2, Chronic Nephritis: (a) Chronic nephritis with contraction (this includes both chronic glomerulonephritis and hypertensive contracted kidney) (table 4). In most instances, the values for serum proteins were normal or but slightly altered late in the disease. Kahn found normal values in all his cases. Edema tended to give the same picture as in acute and subacute nephritis, that is, a lowering of the albumin and total protein with an occasional increase in the globulin. On the whole, however, the changes were much less marked and the correlation between edema and lower serum protein much less evident

than in acute nephritis. These observations are in accord with those of: Reisz; Rowe; Linder, Lundsgaard and Van Slyke; Starlinger and Winands; Fahr and Swanson, and Geill. Occasional exceptions can be found in table 4.

(b) Chronic parenchymatous nephritis. This group includes what is now called lipid nephrosis, both the pure and the mixed types (table 5). These cases showed the greatest quantitative changes in the serum proteins. With few exceptions there was a marked reduc-

TABLE 4.—*The Proteins of Serum and Plasma in Chronic Nephritis with Contraction (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Fibrin, per Cent
Bleibtreu, 1893	6.3 to 8.3	.....	.....	.....	.....
Limbeck and Pick, 1893	.....	.....	.....	Normal	.....
Limbeck and Pick, 1894	7.08 to 8.53	.....	.....	.....	.....
Erben, 1905	Normal	.....	.....	.....	.....
Reisz, 1913	Reduced $\pm$	.....	.....	.....	.....
Epstein, 1914	7.09 to 7.52	2.31 to 4.98	2.53 to 4.77	0.48 to 1.9	.....
Epstein, 1917	6.70	4.31	2.39	1.8	.....
Reisz, 1914	6.65 to 8.72	.....	.....	.....	.....
Rowe, 1917	3.8 to 5.3	1.9 to 3.9	1.4 to 2.0	No reversal	.....
Rowe, 1917	Normal	3.3 to 6.0	1.9 to 2.6	Slight reduction	.....
Rowe, 1917	5.8 to 7.9	.....	.....	.....	.....
Rowe, 1917	6.1 to 7.9	3.6 to 6.1	1.8 to 2.5	Slight reduction	.....
Kahn, 1920	6.52 to 8.67	3.88 to 4.80	2.62 to 3.78	Normal	.....
Linder, Lundsgaard and van Slyke, 1924	Normal	Normal	Normal	Normal	.....
Weltmann and Neumayer, 1925	.....	.....	.....	.....	Increased
Rigler and Rypins, 1924	6.0 to 8.0	3.5 to 5.0	2.0 to 3.0	.....	.....
Von Farkas, 1925	.....	.....	Increased	1.8 to 2.0	.....
Von Farkas, 1925	.....	.....	Normal	2.0 to 2.9	.....
Fahr and Swanson, 1926	4.9 to 7.7	1.5 to 5.1	2.3 to 3.5	0.5 to 2.0	0.3 to 1.3
Kollert and Starlinger, 1922	.....	.....	Normal	.....	High normal
Hiller, McIntosh and van Slyke, 1927	.....	1.77 to 3.48	1.04 to 3.64	0.02 to 1.34	.....
Starlinger and Winands, 1928	4.82 to 8.48	1.5 to 4.03	1.65 to 5.56	Lowered, reversed	Increased
Starlinger, 1928	4.82 to 8.48	1.5 to 4.02	1.65 to 5.56	Lowered, reversed	Increased
Jones, 1929	6.81 to 8.69	3.81 to 5.50	1.54 to 3.18	1.42 to 3.57	0.29 to 0.32

tion in total protein. One of the cases reported by Fahr and Swanson showed a total protein of 3.4 Gm. per hundred cubic centimeters. A similar decrease was found in the albumin fraction. The lowest albumin value (0.63 Gm. per hundred cubic centimeters) was reported by Linder, Lundsgaard and Van Slyke in one of their cases of true nephrosis. In general, the globulin fraction in the cases showed a pronounced increase, and the albumin-globulin ratio was always greatly lowered and usually reversed. In most of the cases, edema was present at some time or other, and in a general way there was a relation between the visible edema and the lower concentration of protein.

Several exceptions to the foregoing observations are encountered. Erben found the total serum protein within normal limits, but there was a distinct lowering, and at times a reversal, of the albumin-globulin

ratio. Kahn found no change in any of the protein fractions. Salvesen's case showed high serum protein (8.97 and 10.73 per cent) marked reduction in albumin (1.69 and 2.56 per cent), and striking increase in globulin (from 7.1 to 8.82 per cent). This patient never had edema.

TABLE 5.—*The Proteins of Serum and Plasma in Chronic Parenchymatous Nephritis (Lipoid Nephrosis, Both the Pure and the Mixed Types (From the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Fibrin, per Cent
Erben, 1905 .....	7.81 to 7.89*	1.92 to 4.76	3.06 to 5.89	0.3 to 1.5	.....
Epstein, 1912 .....	Reduced	Reduced	97% Increased	Reverse	.....
Epstein, 1917 .....	3.92	0.46	3.46	0.13	.....
Epstein, 1923 .....	3.928	0.446	3.486	0.13	.....
Volhard, 1915 .....	Decreased	.....	.....	.....	.....
Kahn, 1920 .....	6.40 to 7.85	4.16 to 4.32	2.24 to 3.59	Normal	.....
Vandorfy, 1921 .....	Decreased	.....	.....	.....	.....
Kollert and Starlinger, 1922	5.61 to 6.85*	Decreased	Increased	Lowered	0.8 to 1.0
Rabinowitch and Childs, 1923	3.6 to 5.8	1.3 to 2.88	2.6 to 2.98	Reverse	.....
Kollert, 1923 .....	Decreased	.....	.....	Lowered	Increased
Linder, Lundsgaard and van Slyke, 1924 .....	3.55 to 7.82	1.6 to 4.8	1.5 to 3.76	0.6 to 2.0	.....
Linder, Lundsgaard and van Slyke, 1924 .....	3.6 to 7.76	0.63 to 4.82	2.24 to 3.47	0.26 to 1.64	.....
Weitmann and Neumayer, 1925	.....	.....	.....	.....	Increased
Rigler and Rypins, 1924 .....	6.1 to 7.22	2.19 to 3.08	3.39 to 5.03	0.4 to 0.9	.....
von Farkas, 1925 .....	.....	.....	Increased	0.8 to 1.2	.....
Kisch, 1922 .....	.....	Low	.....	.....	.....
Munk, 1925 .....	.....	.....	Increased	.....	.....
Kaufmann, 1925 .....	3.48 to 6.1	1.29 to 3.48	1.44 to 3.61	0.35 to 2.1	.....
Govaerts, 1926 .....	.....	.....	.....	Low	.....
Brunetti and Elek, 1925 .....	.....	.....	.....	.....	Increased
Fahr and Swanson, 1926 .....	3.4 to 5.0	1.8 to 2.8	1.4 to 3.3	0.5 to 2.0	0.2 to 0.7
Murphy and Warfield, 1926	.....	.....	.....	Reversed	.....
Klimesch and Weitmann, 1927	.....	.....	.....	.....	Normal
Kollert and Starlinger, 1922	.....	.....	Normal	.....	Increased
Elwyn, 1926 .....	Reduced	Reduced	Increased	.....	.....
Mason, 1926 .....	3.48 to 7.39	Reduced	Variable	Reversed ±	.....
Hiller, McIntosh and van Slyke, 1927 .....	.....	1.02 to 2.4	2.04 to 3.37	0.34 to 1.18	.....
Salvesen, 1927 .....	8.97 to 10.73	1.09 to 2.56	7.1 to 8.82	0.23 to 0.29	0.52†
Bannick and Keith, 1928 .....	3.9 to 6.2	.....	.....	.....	.....
Schultz, Swanson and Zeigler, 1928 .....	3.61 to 5.42	0.98 to 3.22	0.63 to 3.25	Lowered and reversed	.....
Rachmilewitz, 1929 .....	5.38 to 6	2.91 to 3.7	2.3 to 2.97	0.9 to 1.6	.....
Elwyn, 1930 .....	Reduced	Reduced	Increased	.....	.....
Geill, 1928 .....	Reduced	Reduced	Normal	.....	.....

\* Refractometer.

† This case showed no edema.

Group 3, Amyloid Disease of the Kidney: The number of serum protein analyses recorded for this type of renal disease is too small to be conclusive. The few analyses that have been made indicate that the total protein and the albumin in these cases were reduced, and that the globulin was moderately increased (Reisz; Rigler and Rypins; Kisch; Silver and Lindbloom; Elwyn).

Group 4, Hypertensive Contracted Kidney: In practically all instances, the serum protein values were within normal limits (Linder, Lundsgaard and Van Slyke). Von Farkas reported a slight increase in globulin. In none of the cases was there edema.

Group 5, Renal Disease with Uremia: Cases of renal disease with uremia, but without edema, showed normal serum proteins. The uremia, by itself, produced no alteration in the albumin-globulin fractions (Reisz; Rowe; Kollert and Starlinger).

Summary: A review of the literature on the quantitative alterations in serum and plasma proteins in renal disease shows that the most striking changes were found in cases of chronic parenchymatous nephritis (lipoid nephrosis of the pure and mixed types). Here there was a marked reduction in the albumin and total protein, with a high normal or a greatly increased globulin and a high percentage of reversals in the albumin-globulin ratio. The same series of changes, although less marked, were observed in acute and subacute glomerulonephritis. In chronic glomerulonephritis with contraction, normal serum protein values were frequently found, and alterations, when they were encountered, never reached the magnitude of those in lipoid nephrosis. The fibrin values were usually increased, but, aside from the suggestion of Kollert, no particular attention was ever called to this fact. He associated edema with high fibrin values. This will be discussed later.

*Personal Observations.*—Thirty-six cases of renal disease have been studied. These are classified as follows:

1. Acute glomerulonephritis, thirteen cases.
2. Subacute glomerulonephritis, no cases.
3. Chronic glomerulonephritis, twelve cases.
  - (a) Chronic glomerulonephritis with contraction with nitrogen retention.
  - (b) Chronic glomerulonephritis with contraction without nitrogen retention.
  - (c) Lipoid nephrosis, pure and mixed types, one case.
4. Amyloid kidney, two cases.
5. Hypertensive kidney (primary contracted kidney), seven cases.
6. Mercuric chloride nephrosis, one case.

Group 1, Acute Glomerulonephritis: Seventeen analyses were made in thirteen cases (table 6). With two exceptions (cases 5 and 6), the total protein values were lowered. The albumin was generally below normal, falling as low as 1.07 per cent, while the globulin showed a tendency to rise, at one time going to 4.42 per cent. The albumin-globulin ratio was frequently reversed (nine reversals in seventeen analyses). Normal ratios were, however, found in cases 2 and 3. There was a uniform tendency for the nonprotein constituents (determined by the refractometer, the technic of Robertson being followed) to rise, the highest value observed being 2.3 per cent (normal 1.5 per cent).

A low total serum protein and a reversal of the albumin-globulin ratio did not always go together. At times, the total protein was reduced, while the albumin-globulin ratio remained within normal limits (case 2). Conversely, the total protein in one case (case 5), was normal while the albumin-globulin ratio was reversed.

TABLE 6.—*The Proteins of Serum in Acute Glomerulonephritis (Personal Observations)*

Case	Total Protein, per Cent			Albumin, per Cent		Globulin, per Cent		A-G Ratio		Fibrin, per Cent	Non-protein Constituents		Non-protein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	P.S.P.*	Blood Pressure	Albuminuria	Comment
	Refractometer	Kjeldahl	dahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl		per 100 Cc.	per 100 Cc.						
1	6.56	...	2.30	...	4.36	...	0.5	...	...	...	...	36.4	...	21.46	85	94/72	—	Recovering
2	5.60	5.62	4.14	4.22	1.46	1.40	2.8	3.0	...	...	1.5	37.5	...	18.66	70	118/82	Trace	Recovering
3	5.84	...	4.85	...	1.26	...	3.6	...	...	...	1.5	...	...	34.5	47	110/85	Trace	Recovering
4	5.44	5.79	2.30	2.75	3.24	3.04	0.7	0.9	...	...	2.3	240.0	...	119.7	1	210/140	+++	Uremia
5	7.58	7.00	3.16	3.00	4.42	4.00	0.7	0.7	...	...	2.0	184.0	...	79.3	10	156/82	++	Post mortem
6	8.00	...	1.95	...	6.05	...	0.3	...	...	...	...	32.2	...	24.26	85	130/80	Trace	Recovering
7	5.49	...	3.29	...	2.20	...	1.5	...	...	...	1.4	...	...	34.6	32	129/78	++	At height of attack
8	5.93	...	3.57	...	2.36	...	1.5	...	...	...	1.5	...	...	13.5	40	...	+	Recovering
9	6.62	...	3.92	...	2.70	...	1.5	...	...	...	1.6	...	...	62.3	28	160/100	++	At height of attack
10	4.97	3.37	1.57	1.54	3.40	1.83	0.5	0.8	...	...	1.6	...	...	37.3	38	...	+	Recovering
11	4.36	3.46	1.97	1.23	3.29	3.28	0.3	0.6	...	0.1	1.5	60.5	+++	35.0	50	100/110	+++	At height of attack
12	5.49	5.16	3.33	2.71	2.16	2.45	1.5	1.1	...	0.39	1.5	39.0	+	24.0	..	...	++	Recovering
13	5.89	...	3.66	...	2.23	...	1.64	...	...	...	1.5	30.0	—	13.3	56	155/80	+	Recovering
14	6.99	5.23	3.40	2.44	3.59	3.79	0.94	0.64	...	...	2.02	...	...	7.9	?	90/65	+++	Recovering
15	4.32	...	1.63	...	2.69	...	0.64	...	...	...	1.5	...	...	14.0	?	110/60	+++	Recovering
16	4.58	...	1.95	...	2.63	...	0.74	...	...	...	1.46	...	+	14.0	38	140/90	+++	Recovering
17	...	...	...	...	...	...	...	...	...	...	1.4	...	+	...	..	...	.....	At height of attack
Max.	7.58	8.00	4.85	4.22	4.42	4.36	3.0	3.0	0.39	...	...	...	...	...	...	...	...	...
Min.	4.32	3.37	1.63	1.23	1.26	1.40	0.3	0.3	0.10	...	...	...	...	...	...	...	...	...
Aver.	5.67	5.68	3.05	2.45	2.67	3.44	1.34	0.95	0.25	...	1.65	82.5	...	...	...	...	...	...

\* P.S.P. = phenolsulphonephthalein.

TABLE 7.—The Proteins of Serum in Chronic Glomerulonephritis

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Fibrin, per Cent	Non-protein Nitrogen, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	P.S.P.	Blood Pressure	Albuminuria	Comment
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl								
(a) Chronic Glomerulonephritis with Nitrogen Retention																
14	6.54	....	3.85	....	2.69	....	1.4	....	0.18	1.6	....	58.7	1	180/135	++	At height of attack
15	4.68	....	2.24	....	2.44	....	0.9	....	....	1.5	....	92.0	?	185/130	++	At height of attack
16†	4.70	....	2.37	....	2.33	....	1.0	....	....	1.5	....	96.0	?	142/112	++	Slight improvement
17	6.32	5.23	3.51	3.23	2.81	2.00	1.2	1.6	....	2.2	97.8	52.0	?	210/140	++	Uremia
18	5.27	3.19	3.64	3.85	1.63	1.34	2.2	2.9	....	1.6	51.7	38.7	?	108/120	+	At height of attack
19	4.85	3.93	1.66	1.59	3.19	2.34	0.52	0.68	....	1.5	57.0	30.0	6	144/84	++++	Marked edema
19†	5.97	....	2.76	....	3.21	....	0.86	....	....	1.5	....	57.6	1	144/84	+	Just before uremia
20	4.96	3.44	1.17	0.74	3.79	2.70	0.31	0.28	....	1.17	49.5	36.3	65	170/116	++	Slight improvement
21	5.83	5.47	1.70	1.01	4.13	4.46	0.41	0.22	....	2.13	173.3	80.6	38	190/110	++	Post mortem
22	5.41	5.50	2.31	2.64	2.50	2.65	1.2	1.1	....	1.5	39.8	35.46	45	186/104	+	Recovering
23	5.44	5.76	2.11	2.64	3.33	3.12	0.6	0.8	....	1.6	71.4	26.0	48	126/80	+	At height of attack
24	7.65	6.61	4.25	4.40	3.40	2.21	1.3	1.9	1.1	1.9	64.1	17.7	67	126/80	—	Recovering
25	5.22	4.24	1.71	0.97	3.51	3.27	0.5	0.3	....	1.6	141.3	80.3	1	.....	++	Death in uremia
Max.	7.65	6.61	4.25	4.40	4.13	4.46	2.2	2.9	1.1	2.2	173.3					
Min.	4.68	3.93	1.17	0.97	1.63	1.34	0.31	0.22	0.18	1.17	39.8					
Aver.	5.60	5.05	2.61	2.37	2.99	2.67	0.96	1.09	0.64	1.64	82.9					
(b) Chronic Glomerulonephritis Without Nitrogen Retention																
23	3.94	....	2.22	....	1.72	....	1.3	....	....	1.3	....	....	36	158/96	++	At height of attack
24	5.19	....	2.66	....	2.53	....	1.1	....	....	1.4	....	12.55	69	148/98	+	Improving
25	6.13	....	4.76	....	1.37	....	3.5	....	....	1.4	....	6.9	48	178/92	++	Some improvement
26	6.64	5.07	4.47	2.79	2.17	2.28	2.0	1.2	1.7	1.6	36.9	6.5	50	.....	++	Some improvement
(c) A Case of Pure Lipoid Nephrosis																
27	5.24	4.60	1.06	1.10	4.18	3.50	0.23	0.31	....	1.88	....	8.4	65	Normal	++	At height of attack
28	....	4.79	....	1.15	....	3.64	....	0.31	....	....	31.5	10.1	65	Normal	++	At height of attack
29	....	3.79	....	1.72	....	2.07	....	0.83	....	....	39.7	9.0	65	Normal	++	Improving
30	5.93	4.02	1.97	1.18	3.96	2.84	0.40	0.41	....	2.71	35.5	8.8	65	Normal	++	Improving

† Diagnosis confirmed post mortem.

Group 2, Chronic Glomerulonephritis: The cases of chronic glomerulonephritis are arranged in three groups (table 7): (a) those with definite nitrogen retention: (b) those without nitrogen retention, and (c) one case of pure lipid nephrosis.

In the cases of chronic glomerulonephritis with retention, the total protein was moderately reduced, the albumin was lowered, and the globulin was increased. Several extremes are listed in the table. In case 19, the total protein was 3.44 per cent; the albumin, 0.74 per cent; and the globulin, 4.46 per cent, on a second analysis. In case 21 the total protein returned to normal while the patient was improving.

The albumin-globulin ratio was lowered in all cases and reversed in six of the thirteen analyses. The nonprotein constituents (as determined by the refractometer) were slightly increased.

The two cases of chronic glomerulonephritis without retention showed essentially the same changes as those with retention. In one analysis, however, the albumin-globulin ratio reached a high normal value (case 24). In all determinations, the nonprotein constituents (refractometer) fell a little below normal.

The case of lipid nephrosis showed at times a marked reduction in the total protein and in albumin and a pronounced increase in globulin. The albumin-globulin ratio was consistently reversed. This picture is, however, practically the same as that in case 19 (chronic glomerulonephritis with retention).

The development of uremia in no way altered the serum proteins. The nonprotein constituents were, however, increased.

The unusually high nonprotein nitrogen value (173 mg. per hundred cubic centimeters) recorded in the second analysis in case 19 requires some explanation. This was determined on postmortem blood and, as Ikeda and Jacoby have shown, the nonprotein nitrogen, especially the urea nitrogen rises rapidly after death.

Group 3, Amyloid Kidneys (table 8): The changes in the serum proteins in the two cases of advanced renal amyloidosis are recorded in table 8. Both patients died in uremia. No conclusions can be drawn from so small a number of cases, but the unusually low total protein (2.16 per cent) and albumin (0.2 per cent) values are to be noted. There was an associated massive edema. The analysis of the edema fluid is included in table 8.

Group 4, Hypertensive Kidney With Renal Insufficiency (table 9): In six of seven cases of hypertensive renal disease with uremia, the serum proteins were normal, except for an occasional slight reduction of the albumin and total protein. In case 31, however, there was a moderate reduction of total proteins and albumin, with a reversal of the albumin-globulin ratio. There was also an unusual rise in the non-protein value (4.62 per cent). In this case there was a slight edema,

TABLE 8.—*The Proteins of Serum in Renal Amyloidosis with Uremia (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Non-protein Constituents	Non-protein Nitrogen, Mg. per 100 Cc.	Edema	Urea Nitrogen, Mg. per 100 Cc.	P.S.P.	Blood Pressure	Albuminuria
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl							
26	5.78	....	3.08	....	2.70	....	1.14	....	2.01	....	..	134.05	?	104/50	+++++
27	....	....	....	....	....	....	....	....	....	....	—	....	..	....	....
Serum	2.16	2.87	0.20	0.32	1.96	2.55	0.1	0.12	1.5	58.1	++++	....	..	....	....
Pleural fluid	0.160	0.063	?	0.063	?	0	0	....	1.2	47.6	..	....	..	....	....

TABLE 9.—*The Proteins of Serum in Cases of Hypertensive Kidney with Renal Insufficiency (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Non-protein Constituents	Non-protein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	P.S.P.	Blood Pressure	Albuminuria	Edema	Comment
	Refractometer	Kjel-dahl	Refractometer	Kjel-dahl	Refractometer	Kjel-dahl	Refractometer	Kjel-dahl								
29	6.22	....	4.14	....	2.08	....	1.99	....	1.84	....	34.8	26	205/145	++	+	Three days before death
30	6.08	....	4.08	....	2.00	....	2.00	....	1.53	....	40.0	..	250/140	++	+	Early renal insufficiency
31	7.13	....	5.97	....	1.16	....	5.14	....	2.56	....	86.0	..	200+	++	—	Two days before death
32	5.78	....	2.64	....	3.14	....	0.84	....	4.62	....	145.0	..	210/100	++	+	Two days before death
33	6.27	6.63	4.11	4.13	2.16	2.50	1.8	1.6	2.15	209.8	103.1	5	200/140	+++++	+	Post mortem
34	7.37	....	4.61	....	2.76	....	1.67	....	1.67	....	42.0	1	250/180	+	+	Early uremia
35	5.97	....	4.52	....	1.45	....	3.12	....	1.57	93.6	....	30	138/ 68	Trace	++	Decompensated
Max.	7.37	....	5.97	....	3.14	....	5.14	....	4.62	209.8	....					
Min.	6.08	....	2.64	....	1.16	....	0.84	....	1.53	93.6	....					
Aver.	6.40	....	4.29	....	2.11	....	2.37	....	2.28	151.7	....					

but this was no more pronounced than that found in cases with normal protein.

Group 5, Mercuric Chloride Nephrosis (table 10): The single case of bichloride nephrosis included in this series showed a slight drop in albumin and total protein, with some increase in globulin. The albumin-globulin ratio was somewhat lowered, but not reversed. Edema was never observed, and the amount of protein lost in the urine was not great.

Summary: In general, the same series of changes in the serum proteins were found in acute and chronic glomerulonephritis, lipid nephrosis, amyloid disease of the kidney and mercuric chloride nephrosis. The usual picture was a lowering of total protein and of albumin and an increase in globulin, with a lowered and at times reversed albumin-globulin ratio. The occasional exceptions have been pointed out.

TABLE 10.—*Serum Proteins\* in Mercuric Chloride Nephrosis (Personal Observations)*

Case		Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Non-protein Constituents	Edema	Urea Nitrogen, 2Mg. per 100 Cc.	Albuminuria
36	Serum	6.11	3.46	2.65	1.3	2.07	—	140	+
	Urine	0.117	0.10	0.017	5.9	1.88			

\* Determined by refractometer.

In the cases of hypertensive kidney with renal insufficiency, practically normal serum proteins were found except in one case in which the total protein was moderately decreased and the albumin-globulin ratio reversed.

The nonprotein constituents (refractometer) were increased in all the types of renal disease considered, except in chronic glomerulonephritis without retention. The highest values were found in the cases of hypertensive kidney with renal insufficiency.

The fibrinogen values were always slightly increased.

#### THE PROTEINS OF SERUM AND PLASMA IN OTHER DISEASES

*Lobar Pneumonia.*—Observations Recorded in Literature: In cases reported in the literature (table 11), the serum and plasma protein showed definite changes. The total protein was generally lowered, only an occasional normal value being recorded. The albumin showed a consistent reduction, while the globulin and fibrinogen were usually increased. The albumin-globulin ratio was lowered, and reversals were frequently recorded.

Personal Observations: Nineteen analyses in thirteen cases of lobar pneumonia are shown in table 12. With one exception, the total serum

TABLE 11.—*The Proteins of Serum and Plasma in Lobar Pneumonia (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Albumin, per Cent	A-G Ratio	Fibrin, per Cent	Nonprotein Constituents
von Jaksch, 1893.....	7.25 to 11.63	.....	.....	.....	Increased	.....
Limbeck and Pick, 1893	.....	3.18	1.55	.....	.....	.....
Limbeck and Pick, 1894	5.05 to 6.39	.....	.....	.....	.....	.....
Pfeiffer, 1897.....	.....	.....	.....	.....	0.88	.....
Epstein, 1912.....	Lowered	Lowered	Increased	Low reversed	.....	.....
Reisz, 1913.....	Lowered	.....	.....	.....	.....	.....
Reisz, 1914.....	5.69 to 6.39	.....	.....	.....	.....	.....
Schoch,* 1916.....	.....	.....	Increased	.....	.....	.....
Mya-Viglezio,† 1888.....	.....	3.0 to 3.5	3.6 to 4.8	.....	.....	.....
Rowe, 1916.....	5.2	3.7	2.5	Lowered	.....	1.4
Lester, 1922.....	.....	.....	.....	.....	0.73 to 1.45	.....
Gram, 1922.....	.....	.....	.....	.....	Increased	.....
Kollert and Starlinger, 1922.....	Lowered	Lowered	Increased	Lowered	.....	.....
Schindera, 1924.....	.....	.....	Increased	.....	Increased	.....
Foster, 1924.....	.....	.....	.....	.....	Increased	.....
Kollert, 1924.....	Lowered	Lowered	Increased	.....	Increased	.....
Benedetti, 1924.....	.....	.....	.....	.....	Increased	.....
Weltmann and Neumayer, 1925.....	.....	.....	.....	.....	Increased	.....
McLester, Davidson and Frazier, 1925.....	.....	.....	.....	.....	Increased	.....
Lewin, 1927.....	.....	.....	Increased	.....	.....	.....
Klimesch and Weltmann, 1927.....	.....	.....	.....	.....	Increased	.....
Gell, 1927.....	Lowered	Lowered	Increased	.....	.....	.....
Stahlberg, 1928.....	Normal, lowered	.....	.....	.....	.....	.....
Starlinger and Winands, 1928.....	Normal lowered	Lowered	Increased	Reversed	Increased	.....
Berggrün *.....	.....	.....	Increased	.....	Increased	.....
Halliburton *.....	.....	.....	Increased	.....	Increased	.....
Starlinger, 1928.....	.....	.....	Increased	.....	Increased	.....
Corbini, 1928.....	.....	.....	.....	Low	.....	.....
J. Munk, 1929.....	Lowered	Lowered	Increased	Low reversed	.....	.....

\* Quoted by Starlinger and Winands.

† Quoted by Rowe.

TABLE 12.—*The Proteins of Serum in Lobar Pneumonia (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Fibrin, per Cent	Albuminuria	Comment
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl			
1	4.63	5.08	1.03	1.49	3.60	3.59	0.28	0.41	..	Trace	Just before crisis
	5.31	5.40	1.38	1.73	3.93	3.67	0.35	0.47	..	—	12 days after crisis
	5.96	5.28	2.89	1.88	3.07	3.40	0.94	0.55	..	—	17 days after crisis
	6.18	7.08	2.52	2.53	3.66	4.55	0.68	0.55	..	—	25 days after crisis
2	5.43	5.96	1.64	1.79	3.79	4.17	0.43	0.47	..	Trace	Just before crisis
	6.28	6.21	1.85	2.51	4.43	3.70	0.42	0.68	..	—	8 days after crisis
3	6.50	6.45	2.48	2.68	4.02	3.77	0.61	0.71	..	Trace	Just before crisis
	—	6.70	—	3.52	—	3.18	....	1.1	..	—	8 days after crisis
4	7.13	7.36	3.21	3.33	3.92	4.03	0.82	0.82	..	+++	Just after the crisis
5	5.24	....	2.88	....	2.36	....	1.22	....	..	Trace	4 days after crisis
6	5.11	....	2.01	....	....	....	0.64	....	..	—	2 days before crisis
	5.65	....	2.90	....	2.75	....	1.05	....	..	—	8 days after crisis
7	5.52	....	2.08	....	3.44	....	0.60	....	..	..	Before crisis
8	6.03	5.74	3.81	3.68	2.22	2.06	1.7	1.8	0.999	..	3 days after crisis
9	6.24	5.73	2.72	2.19	3.53	3.54	0.77	0.60	..	Trace	During crisis
10	4.96	....	1.99	..	2.97	....	0.67	....	..	Trace	During crisis
11	5.65	....	3.38	....	2.27	....	1.5	....	..	Trace	5 days before crisis
12	5.56	4.45	2.59	1.31	2.97	3.14	0.87	0.41	..	Trace	2 days before crisis
13	6.01	5.02	3.15	1.90	2.86	3.12	1.1	0.6	..	Trace	2 days before crisis
Max.	7.13	7.36	3.81	3.52	4.43	4.55	1.5	1.1			
Min.	4.63	4.45	1.03	1.31	2.22	2.06	0.28	0.41			
Aver.	5.74	5.88	2.47	2.35	3.28	3.53	0.81	0.70			

TABLE 13.—*Changes in Serum and Plasma Proteins in Infections and Infectious Diseases (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Fibrin, per Cent	Disease
Bleibtreu, 1893.....	5.6 to 7.7	.....	.....	.....	.....	Pulmonary tuberculosis
Limbbeck and Pick, 1894	9.17 to 9.05	.....	.....	.....	.....	Empyema
von Jaksch, 1893....	8.25 to 9.3	.....	.....	.....	.....	Typhus
von Jaksch, 1893....	8.27	.....	.....	.....	.....	Puerperal sepsis
von Jaksch, 1893....	9.28	.....	.....	.....	.....	Rheumatic arthritis
Pfeiffer, 1897.....	.....	.....	.....	.....	0.51 to 0.75	Scarlet fever
Pfeiffer, 1897.....	.....	.....	.....	.....	0.17 to 0.45	Typhus
Pfeiffer, 1897.....	.....	.....	.....	.....	0.47 to 0.75	Erysipelas
Pfeiffer, 1897.....	.....	.....	.....	.....	0.62	Puerperal sepsis
Pfeiffer, 1897.....	.....	.....	.....	.....	0.56 to 0.88	Acute poly-arthritis
Winternitz, 1908....	4.79 to 7.21	2.93 to 4.11	1.86 to 2.63	.....	0.33 to 0.49	Syphilis
Oppenheimer and Reisz, 1909	Lowered	.....	.....	.....	.....	Scarlet fever
Reisz, 1913.....	Lowered	.....	.....	.....	.....	Septicemia; arthritis
Reisz, 1914.....	7.75	.....	.....	.....	.....	Sepsis
Schoch,* 1916.....	.....	.....	Decreased	.....	.....	Acute poly-arthritis
Rowe, 1916.....	6.4 to 8.8	3.7 to 5.7	2.7 to 3.4	.....	.....	Endocarditis
Rowe, 1916.....	7.3	5.4	1.9	.....	.....	Typhoid
Rowe, 1916.....	7.5	5	2.5	.....	.....	Syphilis
Alder, 1920.....	.....	.....	Increased, decreased	.....	.....	Tuberculosis
Frisch, 1921.....	.....	.....	.....	.....	Increased	Tuberculosis
Lester, 1922.....	.....	.....	.....	.....	Increased	Septicemia
Lester, 1922.....	.....	.....	.....	.....	Increased	Tuberculosis
Gram, 1922.....	.....	.....	.....	.....	Increased	All infections
Rusznayk, Barát and Kürthy, 1924	.....	.....	Increased	.....	Increased	All acute infections
Schindera, 1924....	.....	Decreased	Increased	.....	Increased	All acute infections
Benedetti, 1924....	.....	.....	.....	.....	Increased	All acute infections
Weltmann and Neumayer, 1925	.....	.....	.....	.....	Increased	All acute infections
McLester, Davidson and Frazier, 1925	.....	.....	.....	.....	Increased	All acute infections
Starlinger, 1925....	.....	Decreased	Increased	.....	.....	Syphilis
Lewin, 1927.....	.....	.....	Increased	.....	.....	All acute infections
Klimesch and Weltmann, 1927	.....	.....	.....	.....	Increased	All acute infections
Gelli, 1927.....	Variable	Decreased	Increased	.....	.....	All acute infections
Wu †.....	8.0 to 9.4	Little change	Increased	Lowered	.....	Syphilis
Wu †.....	6.8 to 10.5	Decreased	Increased	Reversed	.....	Kala-azar
Kapteyn, 1928.....	.....	.....	.....	Low reversed	.....	Active tuberculosis
Starlinger and Winands, 1928	Lowered	Lowered	Increased	Low reversed	Increased	All acute infections
Berggrün *.....	.....	.....	Increased	.....	Increased	Tuberculosis; polyarthritis
Halliburton *.....	.....	.....	Increased	.....	Increased	Poly-arthritis
Starlinger, 1928....	.....	.....	Increased	.....	Increased	All acute infections
Lloyd and Paul, 1928	7.9 to 10.17	Decreased	4.1 to 6.5	Low reversed	.....	Kala-azar
Corbini, 1928.....	.....	.....	.....	Low	.....	Tuberculosis; influenza
J. Munk, 1929.....	Normal, lowered	Decreased	Increased	Low reversed	.....	All acute infections
J. Munk 1929.....	Increased	Slight decrease	Increased	Reversed	.....	Tuberculosis
Jones, 1929.....	7.54 to 8.71	4.07 to 4.86	2.27 to 3.99	.....	0.41 to 0.79	Tuberculosis; infections

\* Quoted by Starlinger and Winands.

† Quoted by Gelli.

protein was moderately lowered, 4.96 per cent being the lowest value observed. There was a more striking reduction in the albumin, while the globulin showed a decided increase. Reversal of the albumin-globulin ratio was encountered in thirteen of the nineteen analyses. It was always present just before and during the crisis. Following the crisis, the total protein values rapidly increased, but the albumin and globulin values were much slower in returning to their normal levels. One case (1) observed for nearly one month after the crisis still showed a reversal of the albumin-globulin ratio. This may be partially explained by the fact that the patient showed a delayed resolution.

TABLE 14.—*Serum Proteins in Acute Infections (Personal Observations)*

Case	Infection	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Albuminuria	Comment
		Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl		
1	Acute rheumatic fever	5.80	5.52	2.75	2.60	3.05	2.86	0.9	0.93	+	Temp. 102-103 F.
2	Pleurisy with effusion	5.50	5.61	2.96	2.86	2.63	2.75	1.1	1.0+	+	Temp. 103 F.
3	Chronic salpingitis	7.41	....	4.55	....	2.86	....	1.50	....	—	Temp. 102-104 F.
4	Typhoid fever	5.18	5.40	2.46	3.28	2.72	3.12	0.66	0.73	+++++	Pyelonephritis
5	Typhoid fever	6.67	....	3.67	....	3.00	....	1.2	....	—	Temp. 104 F.
6	Massive collapse of the lung	6.61	5.33	3.87	2.62	2.74	2.71	1.4	0.97	—	Temp. 104 F.
Maximum		7.41	5.61	4.45	2.86	3.05	3.12	1.50	1.0		
Minimum		5.18	4.33	2.46	2.28	2.63	2.71	0.66	0.73		
Average		6.21	5.47	3.34	2.60	4.17	2.91	1.14	0.90		

The urinary changes were generally insignificant. Most of the cases showed but a trace of albumin, or at most a + result just before and during the crisis, which disappeared immediately afterward. Case 4 was unusual in many ways. There were a heavy and persistent albuminuria, some casts and white blood cells and an occasional red blood cell. All this persisted for some time after the crisis, but finally subsided. The total serum protein was normal, but the albumin-globulin ratio was reversed. No doubt, the kidney was severely damaged.

*Other Infections and Infectious Diseases.*—Observations Recorded in the Literature: In a miscellaneous group of cases of acute infections and infectious diseases collected from the literature (table 13), the values for total serum protein showed considerable variation. In some cases they were normal, in others moderately reduced; while in still others they showed an increase. The albumin values showed practically the same variations. The globulin and fibrinogen values, on the other

hand, were consistently elevated. Albumin-globulin ratios were lowered and at times reversed.

Kala-azar (cases reported by Wu and Lloyd and Paul) showed exceptionally high total serum protein and globulin. The albumin was normal or moderately reduced, while the albumin-globulin ratio was low and reversed. Lloyd and Paul added that such serums had a higher hydrogen ion concentration and a lower iso-electric point than normal.

Personal Observations: In the miscellaneous group of acute infections (table 14), the serum protein changes were in general the same

TABLE 15:—*The Proteins of Serum and Plasma in Heart Disease, With and Without Edema (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Fibrin, per Cent	Edema
Von Jaksch, 1863....	9.63	.....	.....	.....	.....	—
Reisz, 1913.....	Normal	.....	.....	.....	.....	—
Reisz, 1913.....	Lowered	.....	.....	.....	.....	+
Rowe, 1917.....	6.9 to 7.3	4.6 to 5.0	2.7 to 1.9	.....	.....	—
Rowe, 1917.....	6.0 to 1.3	3.4 to 4.7	1.9 to 3.2	.....	.....	+
Kahn, 1920.....	6.69 to 7.17	3.95 to 4.16	2.74 to 3.01	.....	.....	+
Lester, 1923.....	.....	.....	.....	.....	Slight increase	.....
Gram, 1922.....	.....	.....	.....	.....	Normal	.....
Weltmann and Neumayer, 1925.....	.....	.....	.....	.....	Normal	—
Weltmann and Neumayer, 1925.....	.....	.....	.....	.....	Increased	+
McLester, Davidson and Frazier, 1925.....	.....	.....	.....	.....	Increased	.....
Adler and Strausz, 1925.....	.....	.....	Decreased	.....	.....	.....
Fahr and Swanson, 1926.....	5.7 to 7.4	2.5 to 4.2	2.3 to 3.2	0.8 to 1.3	0.2 to 0.3	+
Govaerts, 1926.....	.....	.....	.....	Lowered 0.36	.....	.....
Von Farkas, 1926.....	.....	Normal	Normal	Normal	.....	—
Von Farkas, 1926.....	.....	.....	Increased	Lowered	.....	+
Kilnesch and Weltmann, 1927.....	.....	.....	.....	.....	Slight increase	.....
Gell, 1927.....	Lowered	Lowered	Increased	.....	.....	±
Von Farkas, 1928.....	Normal	Normal	Normal	Normal	Normal	.....
Von Farkas, 1928.....	5.10 to 5.76	2.46 to 3.52	1.92 to 2.22	Lowered	0.32 to 0.58	+
Starlinger and Winands, 1928.....	Normal, lowered	Lowered, normal	Increased, normal	Lowered, reversed	Normal, increased	±
Jones, 1929.....	6.48	2.86	2.59	.....	0.27	.....

as in lobar pneumonia, but less marked. With a single exception, the total protein was reduced, the albumin lowered and the globulin increased. The albumin-globulin ratio was consistently lowered and reversed twice (cases 1 and 4). The serum proteins were determined at the height of the infection. The urine showed no albumin or only a trace, except in case 4, in which there was a severe pyelonephritis. The blood urea nitrogen ranged from 153.5 to 207.6 mg. per hundred cubic centimeters.

*Heart Disease, With and Without Edema.*—Observations Recorded in the Literature: A survey of the literature (table 15) on heart disease both with and without edema shows that the changes in the values for the total serum protein, albumin and globulin were seldom marked. Rarely did these alterations reach the magnitude commonly encountered in some types of renal disease (Reisz; Rowe; Starlinger and Winands).

TABLE 16.—Serum Proteins in Cardiac Decompensation with Edema (Personal Observations)

Case	Total Protein, per Cent			Albumin, per Cent			Globulin, per Cent			A-G Ratio		Non-protein Nitrogen, Mg. per 100 Cc.	Edema	Urea Nitrogen, Mg. per 100 Cc.	Blood Pressure	Albuminuria	P.S.P.	Decompensation
	Refractometer	Kjeldahl	Refractometer	Refractometer	Kjeldahl	Refractometer	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Ratio							
1	5.24	....	1.28	....	3.96	....	0.32	....	1.5	....	....	....	++++	26	190/135	Trace	?	Marked
2	5.37	6.36	3.97	3.86	1.76	2.50	2.3	1.5	1.3	37.3	....	....	++++	20	?	Trace	?	Marked
3	6.50	6.12	4.39	4.23	2.11	1.89	2.1	2.2	1.64	30.3	....	....	++++	?	175/110	—	?	Marked
4	6.35	6.23	2.66	2.79	3.69	3.84	0.72	0.72	1.69	58.8	....	....	++	18.4	222/146	—	46	Moderate
5*	5.65	5.34	2.23	2.87	3.02	2.47	0.87	1.16	1.54	145.6	....	....	++++	?	124/84	Trace	?	Marked; 4+
6	5.11	4.83	4.01	3.68	1.10	1.15	3.6	3.2	1.40	37.1	....	....	+	26	170/145	+	35	jaundice Marked
Max.	6.50	6.63	4.39	4.23	3.69	3.84	3.6	3.2	1.69	145.6	....	....						
Min.	5.11	4.83	1.28	2.79	1.10	1.15	0.32	0.72	1.3	30.3	....	....						
Aver.	5.70	5.86	3.09	3.48	2.61	2.37	1.65	1.76	1.51	61.8	....	....						

\* Diagnosis confirmed at autopsy.

Cases without edema, ascites or hydrothorax generally showed normal values throughout. The presence of edema tended to produce a slight lowering in the albumin and total protein and at times a slight increase in globulin (Rowe; Starlinger and Winands). More marked changes were found in the cases of Fahr and Swanson, Govaerts, and von Farkas. These authors reported reversals of the albumin-globulin ratio.

Von Farkas gave the impression that there is a direct relationship between low albumin, low total protein, increased globulin and edema. No such correlation exists in some of the cases reported by Kahn, Fahr and Swanson, Starlinger and Winands, and von Jaksch. These authors frequently encountered normal and increased values in the presence of marked edema. Geill in his review (1927) concluded that there might be a slight increase in globulin in cases of decompensated heart, regardless of the presence or absence of edema.

The fibrinogen values were generally normal. Occasionally they showed a slight increase.

**Personal Observations:** In the six cases of cardiac decompensation with edema (table 16), the total serum protein showed a moderate reduction, never, however, falling below 5.11 per cent (refractometer) or 4.83 per cent (Kjeldahl). Four of the six cases displayed low albumin, on one occasion as low as 1.28 per cent (case 1). The globulin, with one exception (case 6), was moderately increased. Reversals of the albumin-globulin ratio were found in three of the six cases.

No constant relationship could be established between low serum protein, reversal of the albumin-globulin ratio and edema. The first five of the six cases had practically the same degree of edema (4+), yet, as the table shows, the serum protein and the albumin-globulin ratios showed no similarity. Case 6, which showed the least edema (+), displayed the lowest total protein (4.83 per cent) and an albumin-globulin ratio of 3.2.

Renal function was fair and consistent with the degree of cardiac decompensation and congestion. The urines as a rule never showed more than an inconstant trace of albumin. In case 6 the urine at one time showed a value of 1+.

The total nonprotein values (refractometer) were slightly below normal.

**Pregnancy and Eclampsia.**—In the literature there is no agreement as to the level of the plasma proteins in normal pregnancy with edema and albuminuria (eclampsia and preeclampsia).

**Personal Observations:** In the five cases of preeclamptic toxemia, the serum protein values were all within normal limits (table 17). Several of the cases showed a slight decrease in total serum protein and in the albumin-globulin ratio. Edema and albuminuria produced no

direct change in the serum protein. The kidney was not severely damaged in any instance, and all the patients made a complete recovery. The nonprotein values (refractometer) were normal throughout.

*Malnutrition and Starvation with Edema.*—Observations Recorded in the Literature: From a review of the literature, as well as from his original work, Maver concluded that starvation edemas are due to a

TABLE 17.—*The Proteins\* of Serum and Plasma in Pregnancy with Eclampsia (Personal Observations)*

Case	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Non-protein Constituents	Non-protein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Blood Pressure	Edema	Albuminuria
1 (preeclampsia)	6.49	4.23	2.26	1.87	1.73	37.6	9.65	100/100	++	+++
2	6.76	4.50	2.26	1.99						
2 (preeclampsia)	7.65	4.93	2.72	1.81	1.45	3.92	10	158/112	—	++++
3 (preeclampsia)	6.78	4.91	1.87	2.02	1.19	?	17.7	140/90	+	++++
4 (preeclampsia)	7.73	4.32	3.41	1.20	1.5	28	12.1	154/116	++	—
5 (preeclampsia)	6.77	5.37	1.40	3.88	2	39	10	158/112	—	++++
Maximum	7.73	4.91	3.41	3.83	2	39.2	9.65			
Minimum	6.49	4.23	1.40	1.26	1.45	28	17.7			
Average	7.03	4.71	2.32	2.23	1.57	35.9	11.89			

\* Determined by refractometer.

TABLE 18.—*The Proteins of Serum and Plasma in Deficiency and Dietary Edemas (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Nonprotein Constituents	Nonprotein Nitrogen, Mg. per 100 Cc.	Edema	Comment
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl				
1	3.36	4.19	0.66	0.76	2.70	3.43	0.19	0.22	4.25	....	++++	Dietary deficiency
	3.32	....	1.01	....	2.31	....	0.43	....	1.40	....	++++	Post mortem
2	6.23	6.62	4.00	4.25	2.23	2.37	1.79	1.79	1.84	....	++	No apparent cause
3	....	6.38	....	3.81	....	2.57	....	1.48	....	34.5	++	Dietary deficiency
4	4.22	4.08	2.64	1.94	1.58	2.14	1.67	0.90	1.45	....	+++	Starvation

diet low in protein and high in salt and water. Geill and Jansen found the serum protein greatly reduced in both malnutrition and starvation. Their cases were edematous. Jansen reported a case in which the serum protein fell to 4.03 per cent. J. Munk and Gorter found edema in children who were improperly fed and who were suffering from various types of digestive disorders. In J. Munk's cases, the total serum protein was normal or slightly reduced, the albumin usually reduced and the globulin generally increased. The albumin-globulin ratio was lowered and at times reversed. Bigland encountered edema in pellagra, beri-beri, malaria and starvation.

Personal Observations: In three of the cases listed in table 18 there was a clear history of dietary deficiency or starvation. In case 2, how-

ever, an adequate cause was never found. The edema cleared up spontaneously, but recurred several times later.

The total serum protein was reduced, the values ranging from 3.32 to 6.62 per cent. The albumin was lowered, falling to 0.66 per cent in case 1. The globulin in all cases showed a uniform, moderate increase, while the albumin-globulin ratio was lowered and definitely reversed in case 1. There was also a partial reversal in case 4 (value determined by Kjeldahl). Case 1 was unusual in that it showed the greatest edema, the lowest total serum protein, a pronounced reversal of the albumin-globulin ratio and a nonprotein value (refractometer) of 4.25 per cent.

*Starvation and Marked Emaciation Without Edema.*—Personal Observations: By way of contrast, two cases of starvation with extreme emaciation, but without edema, are given (table 19). These patients took neither food nor water. Perhaps the lack of water was responsible

TABLE 19.—Serum Proteins in Starvation and Marked Emaciation Without Edema (Personal Observations)

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Non- protein Con- stitu- ents	Comment
	Refrac- tometer	Kjel- dahl	Refrac- tometer	Kjel- dahl	Refrac- tometer	Kjel- dahl	Refrac- tometer	Kjel- dahl		
1	6.18	....	4.00	....	2.18	....	1.8	....	1.1	No food or water
2	4.53	....	3.00	....	1.83	....	1.8	....	1.7	Marked emaciation; bili- ary fistula

for the absence of edema. This would be in accord with the experimental work of Frisch, Mendel and Peters, already cited.

The serum proteins showed essentially the same changes as in the deficiency and dietary edemas. The albumin-globulin ratio, although lowered, was never reversed.

*Carcinoma.*—Observations Recorded in the Literature: Most of the reports in the literature on cases of malignant tumors, especially of carcinoma, show a slight lowering of the total serum protein and an increase in globulin. Loeper and Tonnet found the total serum protein low in the early stages of carcinoma, while later it sometimes became as high as 9.2 per cent. This late rise they attributed to a direct transformation of tumor tissue into serum protein. Corbini reported a total serum protein of 12.1 per cent. Loebner reported nearly normal total protein values in most of his cases (average, 7.3 per cent), but two with edema showed low values (4.2 and 4.4 per cent). The albumin was reduced and the globulin increased. Another of his cases without edema presented a total serum protein of 9 per cent.

Loebner further pointed out that although the globulin is usually increased, this increase bears no relationship to the total protein figure.

The fibrinogen was slightly increased in all cases.

**Personal Observations:** There was a striking lack of uniformity in the total protein values (table 20). They ranged from 3.33 to 7.19 per cent. The albumin was reduced in all cases, while the globulin was generally slightly increased, although it fell to 0.93 per cent in case 5. No relation existed between the serum protein values and the degree of edema or ascites. The total nonprotein values (refractometer), with one exception, were a little below normal. There was nothing to indicate serious damage to the kidney in any of the cases. Cases 4 and 5 showed a slight increase in nonprotein nitrogen in the blood and a trace of albumin in the urine. Both, however, were complicated by early stages of peritonitis.

In case 5, in addition to carcinoma of the stomach, marked emaciation was shown, but no edema. The patient had eaten little for about ten

TABLE 20.—Serum Proteins in Carcinoma and Sarcoma (Personal Observations)

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Nonprotein Constituents	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Albuminuria	Edema
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl					
1. Carcinoma of groin....	5.95	5.24	2.62	2.34	3.33	2.90	0.78	0.80	1.34	18.6	?	—	—
2. Carcinoma of ovary....	7.19	....	3.77	....	3.32	....	1.13	....	1.15	....	?	—	+++
3. Carcinoma of stomach	5.36	....	3.78	....	1.58	....	2.32	....	2.31	....	?	—	+++
4. Sarcoma of stomach....	5.74	5.86	3.87	3.56	1.87	2.30	2.07	1.55	1.34	60.9	?	Trace	—
5. Carcinoma of stomach	....	3.33	....	2.40	....	0.93	....	2.6	....	43.1	23.1	Trace	—
Maximum.....	7.19	5.86	3.87	3.56	3.33	2.90	2.32	2.6	2.31	60.9			
Minimum.....	5.36	3.33	2.62	2.34	1.58	0.93	0.78	0.80	1.15	18.6			
Average.....	6.06	4.81	3.51	2.77	2.53	2.04	1.58	1.65	1.54	40.9			

days before the serum proteins were determined, and this may account for a part of the unusual blood picture.

**Lymphogranuloma and Leukemia.**—None of the cases of lymphogranuloma or leukemia reported in the literature showed marked or constant changes in the serum or plasma proteins. The values were generally within normal limits (von Jaksch; Erben; Starlinger and Winands).

**Personal Observations:** The serum proteins were normal in the case of lymphatic leukemia (table 21). In Hodgkin's disease the albumin and total protein values were moderately reduced. The patient had a slight edema of the feet and ankles. The urine was normal in both cases.

**Multiple Myeloma.**—The unusual protein in multiple myeloma was first described by Bence-Jones in 1847 (quoted from Abderhalden). Its presence in the blood serum was described by Decastello, Krausz, and Short and Crawford. The exact amounts were, however, not recorded.

A series of quantitative analyses on serum proteins and Bence-Jones protein are recorded in table 22, taken for the most part from the paper of Bannick and Greene (1929). The total serum protein, albumin and globulin are all subject to great variation. The total protein varies from 5.27 to 13.15 per cent; albumin from 2.50 to 5.26 per cent, and globulin from 0.73 to 9.09 per cent. Jacobson isolated the Bence-Jones protein from the serum and found that it amounted to 7.86 per cent. Doubtless, the high values for total serum protein and globulin are due to

TABLE 21.—*Serum Proteins in Lymphatic Leukemia and Hodgkin's Disease (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Fibrin, per Cent			
	Refractometer		Refractometer		Refractometer		Refractometer		Nonprotein Constituents	Refractometer		
	Kjeldahl		Kjeldahl		Kjeldahl		Kjeldahl			Kjeldahl	Edema	
1. Lymphatic leukemia.....	7.05	....	4.80	....	2.16	....	2.26	....	1.5	..	..	—
2. Hodgkin's disease.....	5.86	....	4.27	....	1.59	....	2.68	....	1.5	..	..	+

TABLE 22.—*Serum Proteins and Bence-Jones Protein in Multiple Myeloma (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Bence-Jones Protein, per Cent
Bannick and Greene, 1929.....	9.00	2.50	6.50	0.38	....
Bannick and Greene, 1929.....	7.30	....	....	....	....
Bannick and Greene, 1929.....	6.00	....	....	....	....
Bannick and Greene, 1929.....	10.54	4.45	6.09	0.73	....
Bannick and Greene, 1929.....	7.00	5.26	1.74	3.02	....
Perlzweig, Delrue and Gischickler, 1928.....	13.54	4.06	9.09	0.45	....
Jacobson, 1917.....	....	....	....	....	7.86
Rowe, 1917.....	6.80	4.8	2.0	2.40	....
Hewitt, 1929.....	6.31	4.35	1.96	2.22	....
Case, 1929.....	5.27	4.54	0.73	6.22	....
Thannhauser and Krausz, 1920.....	6.41	....	....	....	....
Taylor, Miller and Sweet, 1917.....	....	....	....	....	0.2

accumulation of the Bence-Jones protein. Taylor, Miller and Sweet reported a case in which the Bence-Jones protein in the serum amounted to only 0.2 per cent, while Weber, Hutchinson and Macleod found Bence-Jones protein in the urine, but the amount in the blood was too small to show by chemical analysis.

Observations in a Case of Multiple Myeloma Associated with Hyperproteinemia (table 23): The case presented the usual physical and roentgenologic signs of multiple myeloma. The urine contained only a trace of albumin and no Bence-Jones protein. Repeated analyses of the serum and plasma showed a striking elevation of total protein and

globulin, with a normal or slightly reduced albumin. The albumin-globulin ratio was consistently reversed. The fibrinogen was increased.

It would seem logical to assume, in the presence of the high globulin figures, that at least the greater part of the Bence-Jones protein had been carried down with the globulin. Some support is added to this assumption by the fact that after precipitating the globulin by half saturation with ammonium sulphate, the clear supernatant liquid failed to show a clouding when heated to 56 C.

TABLE 23.—*The Proteins\* of Serum and Plasma in Multiple Myeloma with Hyperproteinemia (Personal Observations)*

Case	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Nonprotein Constituents	Fibrin, per Cent
1 Serum.....	13.76	5.81	7.95	0.73	1.7	....
1 Plasma.....	14.13	4.65	9.48	0.49	1.6	....
1 Plasma.....	13.27	3.87	9.40	0.41	1.0	1.45

\* Analysis by refractometer.

TABLE 24.—*Serum Proteins in a Group of Miscellaneous Diseases (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Nonprotein Constituents	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Albuminuria	Edema	Comment
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl						
1*	6.88	....	5.51	....	1.37	....	4.02	...	1.97	214.0	107.1	++	—	Pyelonephritis; death in uremia
2	5.94	....	3.50	....	2.44	....	1.43	...	1.7	....	23.6	++++	—	Stone in the kidney
2	5.96	....	3.00	....	2.96	....	1.01	...	1.4	....	21.5	++++	—	
3	7.26	7.37	5.18	4.85	2.18	2.52	2.3	1.6	1.4	21.8	?	+	—	Lysol poisoning
4*	4.57	....	1.45	....	3.12	....	0.46	...	6.3	....	?	+	—	Acute atrophy of the liver
	6.71	....	3.15	....	3.56	....	0.88	...	2.6	....	....	..	..	Postmortem blood
5*	6.30	6.13	3.81	3.08	2.49	3.05	1.5	1.0	2.2	172.4	78.4	+	++	Pyelonephritis; uremia

\* Diagnosis confirmed at autopsy.

*Diseases of the Liver.*—In cases of diseases of the liver, the total serum protein was normal or slightly reduced (Starlinger and Winands; Abrami and Robert-Wallich; Grenet; Gilbert and Chiray). The albumin was usually reduced (Brunetti and Elek; Abrami and Robert-Wallich; Starlinger and Winands), but occasionally increased (Rusznayák, Barát and Kürthy). The globulin was sometimes normal (Rusznayák, Barát and Kürthy; Brunetti and Elek; Starlinger and Winands), increased or decreased (Adler; McLester, Davidson and Frazier; Lewin; Starlinger and Winands; Rusznayák, Barát and

Kürthy; Schindera; Adler and Strausz). The albumin-globulin ratio was low and frequently reversed (Starlinger and Winands). Fibrinogen showed both an increase and a decrease (McLester; Foster and Whipple; Gram; Isaak-Krieger, Hiege; Scheffer; Weltmann and Neumayer; Benedetti; Klimesch and Weltmann).

*Pyelonephritis and Renal Stone.*—The total serum protein was within normal limits, the albumin reduced and the globulin greatly increased. The albumin-globulin ratio was low and at times reversed (Epstein). The changes in serum proteins were probably due to the infection.

In the cases of pyelonephritis reported by Starlinger and Winands, the total protein was normal, the globulin normal or slightly increased, and the albumin normal or slightly decreased. The albumin-globulin ratio was normal for the most part, but showed a reversal on one analysis. The fibrinogen was increased. Corbini reported a case with renal stone in which the albumin-globulin ratio fell to 1.3.

Personal Observations (table 24): With the exception of case 3 (lysol poisoning) in which the protein values were normal throughout, the total serum protein was lowered, the lowest value (4.57 per cent) being encountered in acute atrophy of the liver. Three of the cases (nos. 2, 4 and 5) showed lowered albumin, increased globulin, a lowering of the albumin-globulin ratio and, in case 4 (acute atrophy of the liver), a pronounced reversal of the albumin-globulin ratio.

#### PROTEINS IN EDEMA FLUIDS

A series of analyses on proteins in noninflammatory edema fluids (subcutaneous fluid and ascitic and pleural fluid) in nutritional disturbances, renal disease, cardiac decompensation and cirrhosis of the liver are given in table 25.

The lowest total protein was found in "war edema" (Jansen, table 25 [c]). The edema fluids of renal disease, cardiac decompensation and cirrhosis of the liver showed practically the same composition. The values for total protein, albumin and globulin were all subject to considerable variation and were not characteristic of any particular disease. Epstein pointed out that the protein content of the edema fluid varies both with the disease and with the location of the fluid. He found the lowest amount of protein in subcutaneous fluids and the highest in pleural fluids, with the abdominal fluids occupying an intermediate position.

In table 25 (a), it is shown that lower protein was found in the edema fluids of nephrosis and amyloid disease of the kidney than in nephritis (Hellmuth, and Beckmann). Beckmann believed that cardiac and cachectic edemas occupy a position midway between those of

TABLE 25.—*Proteins in Edema Fluids (from the Literature)*

Investigator	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	A-G Ratio	Type of Renal Disease and Fluid
<i>(a) Renal Disease with Edema</i>					
Jansen.....	0.578	.....	.....	.....	Nephrosis
Beckmann.....	1.12 to 1.54	.....	.....	.....	Glomerulonephritis
Beckmann.....	0.09	.....	.....	.....	Nephrosis
Beckmann.....	0.08 to 0.16	.....	.....	.....	Amyloid kidney
Beckmann.....	1.18	.....	.....	.....	Acute glomerulonephritis
Pigeaud *.....	.....	.....	.....	0.64 to 0.69	Nephritis; pleural fluid
Hellmuth.....	0.85 to 1.67	.....	.....	.....	Glomerulonephritis
Epstein.....	0.008 to 0.17	0.018 to 0.066	0.079 to 0.104	0.24 to 0.84	Nephritis; anasarca fluid
Epstein.....	1.25 to 3.58	0.37 to 2.11	0.87 to 1.46	.....	Nephritis; pleural fluid
Epstein.....	0.285	.....	0.285	.....	Nephritis; ascitic fluid
<i>(b) Cardiac Decompensation with Edema</i>					
Beckmann.....	0.25 to 1.54	.....	.....	.....	.....
Paykull *.....	.....	0.47 to 0.78	0.38 to 0.72	.....	Ascitic fluid
Csartary.....	.....	0.284	0.280	0.9	Ascitic fluid
Csartary.....	.....	0.337	0.131	2.5	Pleural fluid
Epstein.....	0.1	0.82	0.018	.....	Cardionephritis; anasarca fluid
Epstein.....	1.56 to 4.69	0.07 to 3.05	0.88 to 1.91	.....	Ascitic fluid
<i>(c) Pregnancy and Eclampsia with Edema</i>					
Hellmuth.....	±0.14	.....	.....	.....	.....
<i>(d) Cirrhosis of the Liver with Ascites</i>					
Jansen.....	0.856	.....	.....	.....	.....
Abrami and Robert-Wallich.	1.0 to 2.2	0.5 to 1.1	0.4 to 1.4	.....	.....
Beckmann.....	0.21 to 0.35	.....	.....	.....	.....
Joachim *.....	0.74 to 1.89	.....	.....	.....	.....
Pigeaud *.....	.....	.....	.....	1.41	.....
Paykull *.....	.....	0.76 to 2.56	0.49 to 2.03	.....	.....
Starlinger and Winands....	3.32	1.71	1.61	.....	.....
Epstein.....	0.52 to 3.33	0.19 to 2.00	0.32 to 1.61	.....	.....
<i>(e) War (Nutritional) Edema</i>					
Jansen.....	0.038 to 0.063	.....	.....	.....	.....

\* Quoted by Starlinger and Winands.

nephrosis and nephritis. Csartary thought that the transudation of serum protein, especially albumin, into the tissue fluids is directly related to the height of the blood pressure. This was denied by Hellmuth and Eppinger.

A correlation between the albumin-globulin ratio of edema fluids and that of serum was reported by Mya-Viglezio, Pigeaud, Csartary

TABLE 26.—*Proteins in Edema Fluids (Personal Observations)*

Case	Total Protein, per Cent		Albumin, per Cent		Globulin, per Cent		A-G Ratio		Nonprotein Constituents	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Disease and Kind of Fluid
	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl	Refractometer	Kjeldahl				
1	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Starvation edema
	1.23	.....	0.39	.....	0.84	.....	0.46	.....	1.3	.....	.....	Peritoneal fluid
	0.50	.....	0.01	.....	0.49	.....	0.02	.....	0.9	40.6	13.2	Pleural fluid
	3.32	.....	1.01	.....	2.31	.....	0.43	.....	2.52	.....	22.0	Serum
2	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Chronic glomerulonephritis
	0.64	0.568	?	0.15	?	0.418	?	0.36	1.31	57.0	.....	Ascitic fluid
	4.85	3.93	1.66	1.59	3.19	2.34	0.52	0.68	1.44	54.0	.....	Serum
3	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Chronic glomerulonephritis
	0.66	.....	0.62	.....	0.04	.....	15.0	.....	2.00	.....	.....	Ascitic fluid
4	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Renal amyloidosis
	0.16	0.063	?	0.063	?	—	.....	.....	1.22	47.6	.....	Pleural fluid
	2.16	2.87	0.20	0.32	1.96	2.55	0.1	0.12	1.7	58.1	.....	Serum
5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Hypertensive kidney
	3.83	4.22	2.67	2.46	1.16	1.76	2.38	1.4	2.00	201.0	.....	Ascitic fluid
	6.27	6.63	4.11	4.13	2.16	2.50	1.8	1.6	2.15	209.0	.....	Serum
6	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Metastatic carcinoma of the liver
	1.84	.....	0.98	.....	0.86	.....	1.14	.....	1.63	.....	.....	Ascitic fluid
	5.96	.....	3.78	.....	1.58	.....	2.4	.....	2.31	.....	.....	Serum
7	0.535	0.593	0.045	0.312	0.49	0.231	0.09	1.11	1.35	94.0	.....	Mechanical edema; subcutaneous fluid
8	3.69	.....	1.07	.....	2.02	.....	0.82	.....	2.41	.....	.....	Cardiac decompensation; pleural fluid
9	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Cardiac decompensation
	2.52	2.87	1.45	1.07	1.07	1.80	1.3	0.5	1.3	30.0	.....	Ascitic fluid
	5.73	6.36	3.97	3.86	1.76	2.50	2.3	1.5	1.6	37.0	.....	Serum
10	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Cirrhosis of the liver
	5.28	.....	3.53	.....	1.75	.....	2.01	.....	1.27	.....	.....	Ascitic fluid

(nephritis) and Starlinger and Winands (cardiac edema). Epstein found a close relationship between the globulin percentage of the total protein in serum and that of edema fluids in nephritis. This was not true in his cases of "cardionephritis." Hoffmann was unable to find any correlation between the protein values or ratios of serums and those of edema fluids.

Denis and Minot found practically the same nonprotein values in serum and edema fluids. Epstein, however, found lower nonprotein nitrogen values in edema fluid than in serum.

**Personal Observations:** The results of a series of analyses on edema fluids with the serum protein values, when such were determined, are recorded in table 26. The lowest protein value of pleural fluid was found in a case of renal amyloidosis (0.063 per cent). All of this was albumin (Kjeldahl). The ascitic fluid in chronic nephritis showed a much higher value (0.568 per cent). This is in accord with the results recorded in the literature.

The protein content of the pleural fluid in the case of starvation edema was likewise low (0.5 per cent). Mechanical pressure on the iliac veins by a carcinoma in the pelvic cavity gave rise to an edema of the legs (case 7), the fluid of which was low in protein (0.535 per cent).

The edema (ascitic fluid) accompanying cardiac decompensation had a somewhat higher protein content (from 2.52 to 3.69 per cent).

The highest protein value was found in the ascitic fluid, associated with cirrhosis of the liver (5.28 per cent).

A fair correlation existed between the albumin-globulin ratio of the edema fluids and that of the serum. A reversal of the ratio in one was accompanied by a similar change in the other (cases 1 and 2) and vice versa (case 5). Case 9 was a partial exception. A similar correlation was found in the nonprotein nitrogen values of the edema fluid and the serum. The number of analyses was, however, much too small to justify conclusions.

It is significant that both in the cases listed in table 26 and in those recorded in the literature the edema fluid usually contained both albumin and globulin. Only once was the protein entirely albumin. Either one may predominate.

It appears that the capillaries are permeable to both albumin and globulin.

#### SUMMARY AND COMMENT

*Summary of the Protein Changes in Disease.*—Aside from the cases of hypertensive kidney, in which normal serum protein values were the rule, all forms of renal disease showed a reduction in total protein and albumin and an increase in globulin. The albumin-globulin ratio was usually lowered and frequently reversed. The quantitative protein changes in lipid nephrosis were no more marked than those found in some cases of chronic glomerulonephritis. Amyloid disease of the kidneys and mercuric chloride nephrosis showed essentially the same protein changes as were found in acute and chronic glomerulonephritis and in lipid nephrosis.

Much the same protein picture was found in acute infectious diseases; here also the total protein and albumin were reduced, the globulin was increased, and the albumin-globulin ratio was lowered and occasionally reversed. In lobar pneumonia, the proteins were more markedly affected than in other acute infections. During the crisis, reversal of the albumin-globulin ratio was the rule. On the whole, the picture was often practically the same as that found in acute and chronic glomerulonephritis and lipoid nephrosis.

Cases of cardiac decompensation with edema showed a moderate reduction of total protein and albumin, a variable increase in globulin and a lowered, and at times a reversed, albumin-globulin ratio.

The cases of carcinoma, with a single exception, showed about the same changes.

Cases of starvation with edema presented low total protein and albumin, increased globulin, and a lowered, and at times a reversed, albumin-globulin ratio. In one case, the albumin fell to 0.66 per cent. Several cases of starvation without edema showed essentially the same changes as those with edema.

One of the two cases of pyelonephritis studied showed a moderate reduction of albumin and total protein, a slight rise in globulin, and a lowered albumin-globulin ratio. One case of nephrolithiasis presented much the same picture. In the other case of pyelonephritis, the serum proteins were within normal limits. Similar observations are to be found in the literature.

Normal protein values were found in the one case of lymphatic leukemia that was studied, while moderately reduced albumin and total protein values were found in an advanced case of Hodgkin's disease. The albumin-globulin ratio was also lowered.

A single case of acute atrophy of the liver (confirmed at autopsy) displayed lowered albumin and total protein, marked increase in globulin and a reversal of the albumin-globulin ratio.

A case of multiple myeloma showed markedly increased total protein and globulin, with normal or moderately reduced albumin. The albumin-globulin ratio was consistently reversed.

From my own observations, as well as from data recorded in the literature, it would seem that a decrease of the total serum protein and albumin, accompanied by an increase in globulin and a lowered or reversed albumin-globulin ratio, is not distinctive of lipoid nephrosis or of acute, subacute or chronic glomerulonephritis. The occurrence of similar, and at times nearly identical, changes in a group of diseases so unrelated as acute infections, lobar pneumonia, cardiac decompensation, carcinoma, acute atrophy of the liver and dietary deficiency furnishes support for this observation. Because of the marked

similarity in the serum protein pictures in lobar pneumonia and acute nephritis, Bookman, Findlay, and Tileston and Comfort stated that the impairment of renal function which they found in pneumonia was due to acute nephritis. Normal renal function in pneumonia was found, however, by Reimann, Longcope and Peters, Lewis and Frothingham.

On the whole, it seems logical to conclude that a reduced or reversed albumin-globulin ratio is not pathognomonic for any one disease. Any infection or intoxication (Hurwitz and Whipple), as well as the diseases enumerated, and even the injection of an irritant (von Farkas) can cause it. Corbini suggested that the albumin-globulin ratio is merely an index of the amount of tissue destruction, while Hurwitz and Whipple attributed the lowering and reversal to a metabolic disorder.

*The Cause of the Changes in the Serum Proteins.*—There is much uncertainty regarding the cause of the protein alterations in disease. In some of the nephropathies, e. g., lipoid nephrosis, the low total serum protein and albumin may be due to loss of albumin in the urine (Epstein and Vandorfy). Kollert, Linder, Lundsgaard, and van Slyke, Fahr and Swanson, Govaerts and Geill granted that while loss of albumin in the urine may be a factor, it fails to explain the entire picture. Kollert pointed out that lobar pneumonia without albuminuria frequently shows practically the same changes in serum proteins as does nephrosis. The analyses on serum proteins in renal disease and in lobar pneumonia reported in this paper are entirely in accord with the observations of Kollert. In none of the cases of lobar pneumonia listed in table 12 was more than a trace of albumin shown, yet the total protein was low and the albumin-globulin ratio was reversed. Several of the cases of acute infection reported, those of carcinoma, those of cardiac decompensation with edema and those of dietary deficiency showed similar changes. Fahr and Swanson found the same conditions in a case of hyperpiesia without albuminuria. Govaerts found an albumin-globulin ratio of 0.36 in a cardiac case with edema but no albuminuria.

Conversely, in preeclamptic toxemia with persistent heavy albuminuria, there was a normal or nearly normal serum protein. A moderate amount of albuminuria in the case of hypertensive kidney disease caused no alteration in the serum proteins.

The simple loss of albumin in the urine does not explain the increase in serum globulin.

Dilution of the serum (hydremia) has also been suggested as a cause for the lowered total protein and albumin in some forms of renal disease (von Jaksch; Reisz; Rowe; Erben; Askanazy; Strauss; Veil). The more recent work, however, of Schwartz and Kohn, of Linder, Lundsgaard, van Slyke and Stillman, and of Brown and Rown-

tree shows a normal and at times a decreased blood volume in nephritis and nephrosis. The low protein therefore represents a true loss.

Fahr and Swanson reached practically the same conclusion, adding that even if there were a dilution it would fail to explain the increase in globulin.

A disturbance or alteration in protein production was suggested by Linder, Lundsgaard and van Slyke.

The lowering of the serum protein values in lobar pneumonia and in acute infections is due to a thinning of the blood, according to von Jaksch, Askanazy and Rowe. It is difficult, however, to explain the increased globulin values on this basis, unless it is assumed that there is an increased globulin production under these conditions. Albuminuria fails to explain the low serum albumin, for in the majority of the cases the urines were protein-free. Occasionally one would show a faint trace. Starlinger and Winands found the same in their cases. In lobar pneumonia there is, of course, some loss of protein in the alveolar exudate. It seems more probable that the protein alterations are due to the infection and intoxication (Hurwitz and Whipple) or to the degree of tissue destruction (Corbini).

According to von Jaksch, Askanazy, Strauss, Veil and Brown and Rowntree, there is an increased blood volume in cardiac decompensation with edema. This thinning of the blood might therefore explain the low albumin and total protein found in this condition, but not the increased globulin. Chiray stated that the blood volume is at times decreased in cardiac cases with edema.

There is an increase in blood volume in carcinoma (Galehr; von Jaksch; Loeper and Tonnet), pregnancy with edema (Zangemeister; Dienst) and malnutrition with edema (Jansen). In malnutrition, the lack of protein in the diet no doubt plays a large part in the causation of low serum protein.

The outstanding difficulty in attempting to explain the serum protein alterations as due to a dilution or thinning of the serum is that, while this no doubt accounts for the lower total protein and albumin, it fails to explain the increased globulin.

*The Rôle of Plasma and Tissue Proteins in the Causation of Edema.*—A direct relationship between low serum proteins and visible edema has been suggested by Reisz, Rowe, Facio, Csartary, Rabinowitch and Childs, Bookmann, Starlinger and Winands, Mason and Epstein. The serum proteins have a small but significant osmotic pressure (Starling; Verney; Cope), and a decrease in their concentration might lower their osmotic pressure to a point at which it would be a factor in the production of edema (Frisch, Mendel and Peters; Epstein; Fishberg; Govaerts).

In the original work reported in this paper, no constant relationship could be established between low serum proteins and edema. Low serum proteins were frequently found with edema, but the association was by no means constant. The same conclusion was reached by: Linder, Lundsgaard and van Slyke; Fahr and Swanson; Bannick and Keith; von Farkas; Schwartz and Kohn, and Cope. Fahr and Swanson, for example, had a case of acute nephritis with marked edema that showed a total serum protein of 8.4 per cent, albumin of 5.2 per cent and globulin of 3.2 per cent. Linder, Lundsgaard and van Slyke at times found no edema when the total serum protein had fallen to 4.5 per cent. They pointed out that although the colloid osmotic pressure is often low in nephritis and nephrosis, no constant parallelism can be demonstrated between this lowered osmotic pressure and edema. Cope added that there is no relation between colloid osmotic pressure and edema of cardiac origin. J. Munk, von Jaksch and Nonnenbruch found high serum protein values in cases with severe edema.

This lack of correlation between low serum protein and edema, which was first pointed out in the summary of the analyses on renal diseases, becomes even more apparent as the serum protein values found in other diseases are considered. In lobar pneumonia, for example, the total protein fell just as low as in the average case of glomerulonephritis and lipid nephrosis, yet no edema developed. Conversely, the same low total protein values were accompanied by edema in all the cases of cardiac decompensation. In several of the cases of pre-eclamptic toxemia, moderate edema was found in the presence of a nearly normal total protein. Malnutrition and starvation gave practically the same serum protein picture regardless of edema.

It was found, however, as previously suggested by Linder, Lundsgaard and van Slyke, that total protein values of 4 per cent and less were constantly associated with edema regardless of the type of renal disease.

In the analysis reported here, low serum protein was generally accompanied by low albumin and a lowered or reversed albumin-globulin ratio. This relationship, however, was not constant. In one case of chronic glomerulonephritis (no. 23) there was a total serum protein of 3.94 per cent, but the albumin-globulin ratio was not reversed. Conversely, a lowered and at times reversed albumin-globulin ratio was occasionally associated with normal total protein.

Low serum albumin is the main cause of edema, according to Barker and Kirk and Dienst. Govaerts, von Farkas and Cope concluded that the "specific colloid osmotic pressure" has a direct relation to the magnitude of the albumin-globulin ratio. A low albumin-globulin ratio

therefore indicates a low "specific colloid osmotic pressure," and this causes edema (Facio; Ruzsnyák, Barát and Kürthy).

The original observations reported here did not show a constant relationship between edema and low albumin-globulin ratio. In the cases of renal disease studied, low and reversed albumin-globulin ratios were often not associated with edema, while nearly normal ratios frequently accompanied marked edema. In lobar pneumonia, a few severe acute infections and acute atrophy of the liver, in which the albumin-globulin ratio was strikingly reversed, no edema could be made out. In preeclamptic toxemia, malnutrition, and cardiac decompensation, edema occurred irrespective of the magnitude of the albumin-globulin ratio.

Albumin values of 0.8 per cent and less, as pointed out by Barker and Kirk, were, however, always accompanied by edema. Kohman, Denton and Kohman, Maver and Frisch, Mendel and Peters, in their experimental work, found that nutritional edema was directly dependent on low protein and high water intake. The same has repeatedly been observed with edema occurring during famine and war. Both factors must be operating. In the cases of malnutrition reported in this paper, no edema developed when the patient took neither food nor water. Frisch, Mendel and Peters pointed out that while the serum protein is lowered as much as 40 per cent and the colloidal osmotic pressure necessarily falls, these phenomena are not wholly responsible for the edema. Rather the low serum protein determines a tendency toward water retention, which is probably influenced by other factors.

Whether edema of the tissues is accompanied by "edema of the blood" (hydremia) is a disputed point. In nephritis with edema there is a thinning of the blood (Bright; von Jaksch; Erben; Reisz; Askanazy; Rowe; Strauss; Veil). This is denied by Linder, Lunds-gaard, van Slyke and Stillman, by Brown and Rowntree and by Schwartz and Kohn. The same disagreement is found as regards cardiac decompensation with edema (Chiray; von Jaksch; Askanazy; Strauss; Veil; Brown and Rowntree). On the other hand, hydremia has been described as occurring in febrile diseases (von Jaksch; Askanazy; Rowe) and in carcinoma (Galehr; von Jaksch; Loeper and Tonnet). No edema is present in these conditions.

From the available evidence, therefore, it would appear that no constant relationship exists between tissue edema and hydremia.

It has been suggested by Maxwell, by Achard, Ribot and Leblanc, by Dyke and by Stepp that there is a direct relationship between the amount of blood cholesterol and edema in acute nephritis. Maxwell added that no such correlation exists in chronic parenchymatous nephritis. Strauss thought that edema in nephritis may be due to an

altered cholesterol-lecithin ratio. Hahn and Wolff, Beumer, and Schwartz and Kohn were unable to find any relationship between blood lipoids and edema. Von Farkas showed that the addition of lecithin and cholesterol reduces the specific colloid osmotic pressure of the serum. A reciprocal relationship between the serum proteins and fats was found by Fishberg. As the colloid osmotic pressure fell, secondary to the loss of serum proteins, the lipid content of the serum rose in an attempt to build up the lowered osmotic pressure. Kollert attributed much of the edema of nephritis to an increase of hydrophil fibrin in both the blood and the tissues.

In considering edema from the standpoint of protein, it is first of all necessary to recognize both blood and tissue proteins as constituting a part of a highly sensitive hydrophil colloid system. Components of such a system display a small but definite osmotic pressure and an equally important imbibition or swelling pressure. Their physical structure may be altered and their action modified by changes in hydrogen ion concentration, by the anions and cations enumerated in the Hofmeister series and by adsorption of substances on their surfaces. All these can influence the degree of hydration of the colloid. Water bound by the colloids can again be lost (syneresis) (Gortner).

The colloids of the blood are separated from the colloids of the tissue spaces by the capillary wall, which possesses many properties common to a dialyzing membrane. The colloids of the tissue spaces are in turn separated from those in the cell by the cell wall, which may act as an osmotic membrane (Schade and Menschel).

The membranes themselves are probably made up of hydrophil colloids and would accordingly be sensitive to all the factors just enumerated.

Under normal conditions, a Donnan equilibrium exists around the capillary or dialyzing membrane. This results in an unequal distribution of electrolytes on the two sides of the membrane and consequently an osmotic system is established. By this osmotic action, water is pulled from the tissues into the blood (Rusznayák, Barát and Kürthy). In this the serum colloids no doubt play a small but definite rôle.

Under abnormal conditions resulting in the production of edema, many changes take place in the colloids of the blood, membranes and tissues. The imbibition capacity of the serum colloids may be in some way modified or increased (Thomas and Andrews) or their degree of dispersion altered, owing to the presence of some foreign substance in the blood.

The capillary wall, owing to its component hydrophil colloids, may have its permeability altered by this same substance (Cohnheim; Reisz; Georgopulos; Schlayer; Volhard). Such a possibility was denied by

Kollert and by Engel and Orszag. Fair evidence in favor of an increased permeability of the capillary membrane is furnished by the fact that the edema fluid in all cases contains an excess of protein (both albumin and globulin).

As a result of this altered permeability, the entire osmotic balance around the capillary wall is upset.

The same foreign substance can well alter the imbibition capacity of the tissue colloids, causing them to take up more water (Thomas and Andrews). The entrance of the serum proteins into the tissue fluids may likewise influence imbibition and thus play a part in edema (Eppinger; Schade and Menschel; Kisch).

The water thus imbibed by the tissue colloids is held ("bound") in a different way from that in which it is held under normal conditions (Steggerda). There is now a much greater tendency for the colloid to hold tightly to the imbibed water.

Finally, owing probably to some change in the surrounding media or to some alteration in the tissue colloid itself, the bound water is released and then lies free in the tissue spaces (syneresis).

A few independent experiments were undertaken along lines similar to those followed by Steggerda in his work on bound water. Muscles were taken from edematous frogs, thin unstained frozen sections made, and several hundred of the individual muscle bundles measured. These were compared with an equal number of measurements made on muscles of normal frogs. Without exception, the muscle bundles of the edematous frogs showed a greater diameter than those of the normal frogs. This difference ranged from 22 to 30 per cent. It was further observed that swollen frogs that showed large amounts of free water beneath the skin and between the muscles showed less swelling of muscle bundles than did those frogs that were distinctly swollen, but that had little free water beneath the skin or between the muscles.

The cause of edema in these frogs is unknown. The kidneys were studied in all cases, but these showed nothing abnormal.

While it is admitted that it is unsafe to attempt to interpret human edema in terms of edema observed in a frog, it is nevertheless plausible to assume, from the known physical and chemical properties of colloids, as well as from experiments in blood and tissue colloids on human material (especially the work of Schade and Menschel), that in edematous states, some of the excess water is held ("bound") by the tissue colloids, while the remainder lies free in the tissue spaces.

The foregoing discussion of edema gives merely a picture of colloid changes that may possibly be taking place under certain abnormal conditions. The causes, or inaugurating factors, of such changes are not known. No doubt they are many and varied.

From the original work and observations recorded here, as well as from some data gathered from the literature, it seems fair to assume that alterations in serum proteins do not in themselves adequately explain edema of any kind. They reflect, rather than inaugurate, the changes giving rise to edema.

It might also be suggested that nothing is to be gained from the separation of serum protein into its albumin and globulin fractions. This separation is entirely arbitrary and artificial and does not represent the protein as it existed in the body. Perhaps there is only a single large protein aggregate in the serum, which, because of its inherent colloidal properties, may be so altered in disease that it responds differently when subjected to the action of different salts in the test tube.

#### CONCLUSIONS

In all forms of renal disease considered here, except hypertensive kidney, in which normal serum protein values were found to be the rule, the total protein and albumin were lowered, the globulin was increased, and the albumin-globulin ratio was lowered and frequently reversed. Values approaching the normal were infrequently found. There were no protein changes pathognomonic for any one type of renal disease.

Lobar pneumonia gave a picture very much like that found in renal disease, in that there was a marked reduction in albumin and total protein, a distinct increase in globulin and a persistent reversal of the albumin-globulin ratio. This was true only during the crisis. Other acute infections showed the same, but less marked changes.

In cardiac decompensation with edema, there was a moderate reduction in albumin and total protein, with a moderate increase in globulin and a lowered, and at times reversed, albumin-globulin ratio.

In advanced carcinoma, the albumin was constantly reduced, while the globulin was normal or slightly increased. With a single exception, the total protein was lowered. The albumin-globulin ratio was slightly reduced; on one occasion it was reversed.

In malnutrition with edema, the albumin and total protein were moderately reduced, while the albumin-globulin ratio was moderately lowered. Starvation without edema gave the same picture. In one case with massive edema, unusually low albumin and total protein values with increased globulin and a striking reversal of the albumin-globulin ratio, were found.

Practically normal values were found in a case of lymphatic leukemia, while a case of advanced Hodgkin's disease showed normal globulin, but a moderate lowering of albumin and total protein.

Unusually high values for globulin and total protein with normal or moderately reduced values for albumin, were found in a number of analyses in a case of multiple myeloma.

Acute atrophy of the liver, kidney stone and one case of pyelonephritis showed a moderate lowering of albumin and total protein with some elevation in globulin. The albumin-globulin ratio was reversed in acute atrophy of the liver. Normal protein values were found in a second case of pyelonephritis.

Normal protein values were the rule in preeclamptic toxemia.

Analysis of a limited number of anasarca, ascitic and pleural fluids showed the presence of both albumin and globulin. The protein content varied with the type of disease and possibly also with the location of the fluid.

A comparison of the results secured by the refractometer and by the micro-Kjeldahl method showed that they agree fairly well except as concerns lipemic milky serums. Here the total protein and at times the globulin values given by the refractometer are much too high.

Marked lowering and reversal of the albumin-globulin ratio was not pathognomonic for any one disease or group of diseases. It appeared to be more directly related to the degree of infection and intoxication or to that of tissue destruction.

No constant correlation could be established between edema and low serum protein, or between edema and reversal of the albumin-globulin ratio. Neither was there any constant relationship between low serum protein and reversal of the albumin-globulin ratio.

#### BIBLIOGRAPHY

- Abderhalden, E., and Rostoski, O.: Beitrag zur Kenntnis des Bence-Jonesschen Eiweiskörpers, *Ztschr. f. physiol. Chem.* **46**:125, 1905.
- Abrami, P., and Robert-Wallich: Modifications du sérum sanguin au cours des cirrhosis du foie avec ascite. Inversion du rapport serines-globulines, *Compt. rend. Soc. de biol.* **101**:291, 1929.
- Achard, C.; Ribot, A., and Leblanc, A.: Le coefficient lipémique dans les hydropies, *Compt. rend. Soc. de biol.* **82**:339, 1919.
- Adler, A.: Der Einfluss der Leber auf die Wasserausscheidung, *Klin. Wchnschr.* **2**:1980, 1923.
- Anhaltspunkte für die Prognosenstellung der Lungentuberkulose aus refraktometrischen und viskosimetrischen Serumuntersuchungen, *Ztschr. f. Tuberk.* **31**:10, 1919-1920.
- Adler, E., and Strausz, L.: Beitrag zum Mechanismus der Bilirubinreaktion im Blutserum, *Ztschr. f. d. ges. exper. Med.* **44**:9, 1924-1925.
- Askanazy, S.: Ueber den Wassergehalt des Blutes und Blutserums bei Kreislaufstörungen, Nephritiden, Anämien, und Fieber nebst Vorbemerkungen über die Untersuchungsmethoden und über den Befund unter physiologischen Verhältnissen, *Deutsches Arch. f. klin. Med.* **59**:385, 1897.

- Ueber die diagnostische Bedeutung der Ausscheidung des Bence-Jones'schen Körpers durch den Harn, *ibid.* **68**:34, 1900.
- Bannick, E. G., and Greene, C. H.: Renal Insufficiency Associated with Bence-Jones Proteinuria, *Arch. Int. Med.* **44**:486, 1929.
- and Keith, N. M.: The Treatment of Nephritis and Nephrosis with Edema, *J. A. M. A.* **91**:1944, 1928.
- Barker, H. M., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *Arch. Int. Med.* **45**:319, 1930.
- Barlocci, A.: Physikalisch-chemische Veränderungen des Blutes nach Para und Thorakocentese, *Ztschr. f. klin. Med.* **73**:278, 1911.
- Beckmann, K.: Ödemstudien, *Deutsches Arch. f. klin. Med.* **135**:39, 1921.
- Benedetti, F.: Le deviazioni della formula proteica del sangue; la determinazione della fibrinemia; a scapo clinico; rivista ricostruttiva con ricerche originali, *Arch. di path. e clin. med.* **4**:213, 1925; abstr., *Ber. u. d. ges. Physiol. u. exper. Pharmacol.* **32**:876, 1925.
- Benzür, J.: Das Verhalten des Refraktionswertes des Blutserums nach Aufnahme von Kochsalz, *Ztschr. f. klin. Med.* **67**:164, 1909.
- Berggrün, quoted by Starlinger and Winands.
- Berglund, H.: Personal communication to the author.
- Beumer, H.: Ueber nephrotische Hypercholesterinämie und die Frage ihrer diätetischen Beeinflussbarkeit, *Arch. f. Kinderh.* **68**:105, 1921.
- Bigland, A. D.: Oedema as a Symptom of So-Called Food-Deficiency Diseases, *Lancet* **1**:243, 1920.
- Bing, H. I., and Heckscher, H.: Untersuchungen über Lipämie, *Biochem. Ztschr.* **149-150**:79, 83 and 90, 1924.
- Bleibtreu, L.: Ueber die quantitativen Verhältnisse der Eiweisskörper im Blutserum von Kranken, *Deutsche med. Wchnschr.* **19**:1167, 1893.
- Böhme, A.: Ueber die Schwankungen der Serum-Konzentration beim gesunden Menschen, *Deutsches Arch. f. klin. Med.* **103**:522, 1911.
- Bookman, A.: A Study of Renal Function in Patients Convalescing from Acute Fevers, *Arch. Int. Med.* **20**:112, 1917.
- Brown, G. E., and Rowntree, L. G.: The Volume and Composition of the Blood and the Changes Incident to Diuresis in Cases of Edema, *Arch. Int. Med.* **35**:129, 1925.
- Brunetti, H., and Elek, L.: Untersuchungen über physikalisch-chemische Veränderungen im Blut nach experimentellen Fieber, mit besonderer Berücksichtigung von Leberkranken, *Ztschr. f. d. ges. exper. Med.* **47**:165, 1925.
- Chiray, M.: Dilution et concentration du sang, *Presse méd.* **16**:19, 1908.
- and Demanche: Valeur des indications fournies par le refractometre dans la mesure des albumines du serum et des sérosites, *Compt. rend. Soc. de biol.* **63**:235, 1907.
- Cloetta, M.: Ueber die Genese der Eiweisskörper bei der Albuminurie, *Arch. f. exper. Path. u. Pharmacol.* **42**:453, 1899.
- Cohnheim, J., and Lichtheim, L.: Ueber Hydrämie und hydrämisches Plethora, *Virchows Arch. f. path. Anat.* **69**:106, 1877.
- Cope, C. L.: The Osmotic Pressure of the Blood Proteins in Nephritis, *Quart. J. Med.* **22**:91, 1928.
- Corbini, G.: Il comportamento del quoziente globuline labili nel siero del sangue in condizioni normal sieroproteine e patologiche, *Hematologica* **9**:183, 1928.
- Csartary, A.: Ueber Globulinurie, *Deutsches Arch. f. klin. Med.* **48**:358, 1891.
- Decastello, A.: Beiträge zur Kenntnis der Bence-Jonesschen Albuminurie, *Ztschr. f. klin. Med.* **67**:319, 1909.

- Weitere Beobachtungen über Bence-Jonessche Albuminurie bei Leukemia, Wien. Arch. f. inn. Med. **1**:335, 1920.
- Denis, W., and Minot, A. S.: The Nonprotein Constituents of Edema Fluids, Arch. Int. Med. **20**:879, 1917.
- Denton, M. C., and Kohman, E.: Feeding Experiments with Raw and Boiled Carrots, J. Biol. Chem. **36**:249, 1918.
- Diebold: Zur Frage der Lipoidnephrose, Deutsche med. Wchnschr., 1927, vol. 55; abstr., Centralbl. f. allg. Path. u. path. Anat. **47**:341, 1930.
- Dienst, A.: Kritische Studien über die Pathogenese der Eklampsie auf Grund pathologisch-anatomischer Befunde, Blut- und Harnuntersuchenp eklamptischer Mütter und deren Früchte, Arch. f. Gynäk. **65**:369, 1902.
- Die Eiweissstoffe im Blutplasma unter normalen Verhältnissen in der Schwangerschaft und bei Eklampsie, ibid. **109**:669, 1918.
- Dyke, S. C.: On the Pathology of Nephritis with Edema, as Illustrated by Six Cases, Quart. J. Med. **18**:77, 1924-1925.
- Ellinger: Das Vorkommen des Bence-Jones'schen Körpers im Harn bei Tumoren des Knochenmarks und seine diagnostische Bedeutung, Deutsches Arch. f. klin. Med. **62**:255, 1899.
- Elwyn, H.: Nephritis, New York, The Macmillan Company, 1926.
- The Pathogenesis of Lipoid Nephrosis, Arch. Int. Med. **38**:359, 1926.
- Some Present-Day Concepts of Nephritis, Am. J. M. Sc. **179**:149, 1930.
- Engel, K., and Orszag, O.: Untersuchungen über den Zusammenhang des Blutserums und der serösen Flüssigkeitsergüsse, Ztschr. f. klin. Med. **67**:176, 1909.
- and Scharl, P.: Die Konzentrationsveränderung des Blutserums nach Wasseraufnahme, Ztschr. f. klin. Med. **60**:225, 1906.
- Eppinger, H.: Pathologic und Therapie des menschlichen Ödems, Berlin, J. Springer, 1917.
- Epstein, A. A.: A Contribution to the Study of the Chemistry of Blood Serum, J. Exper. Med. **16**:719, 1912.
- Further Studies on the Chemistry of the Blood Serum, ibid. **17**:444-452, 1913.
- Studies on the Chemistry of Serous Effusions, ibid. **20**:334, 1914.
- Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation, Am. J. M. Sc. **154**:638, 1917.
- Further Observations on the Nature and Treatment of Chronic Nephrosis, ibid. **163**:167, 1922.
- and Lande, H.: Studies on Blood Lipoids, Arch. Int. Med. **30**:561, 1922.
- Erben, F.: Zur Kenntnis der chemischen Zusammensetzung lymphämischen Blutes, Ztschr. f. klin. Med. **40**:282, 1900.
- Studien über Nephritis. Ibid. **57**:39, 1905.
- Eufinger, H., and Spiegler, R.: Die Kolloidstruktur des Plasmas während der Gestation, Arch. f. Gynäk. **133**:465, 1928.
- Facio, L. J.: Die biologische Bedeutung der Osmose bei der Entstehung der Ödeme der Nierenkranken, Semana med. **27**:73, 1920; abstr., Ber. d. ges. Physiol. u. exper. Pharmakol. **2**:322, 1920.
- Faconi, G.: Zur Ödemfrage, genuine Nephrose und idiopathisches Ödem, Jahrb. f. Kinderh. **110-111**:12, 1925-1926.
- Fahr, F.: Beiträge zur Frage der Nephrose, Virchows Arch. f. path. Anat. **239**:32, 1922.
- Fahr, G., and Swanson, W. W.: The Quantities of Serum Albumin, Globulin and Fibrinogen in the Blood Plasma in Acute and Chronic Nephropathies, Arch. Int. Med. **38**:510, 1926.

- von Farkas, G.: Ueber die Wirkung des Albumin-Globulin-Quotienten auf den osmotischen Druck des Serums, *Ztschr. f. d. ges. exper. Med.* **50**:410, 1926.  
 Studien über den kolloidosmotischen Druck des Serums, *ibid.* **53**:666, 1927.  
 Zur Pathologie der Bluteiweisskörper, *ibid.* **63**:64, 1928.
- Findlay, L.: Association of Pneumonia and Acute Bright's Disease, *Arch. Dis. Childhood* **3**:148, 1928; abstr., *J. A. M. A.* **91**:525, 1928.
- Fishberg, E. H.: The Relations of the Serum Proteins and Lipoids to the Osmotic Pressure, *J. Biol. Chem.* **81**:205, 1929.
- Folin, O., and Wu: A System of Blood Analysis, *J. Biol. Chem.* **38**:81, 1919.
- Foster, D. P.: A Clinical Study of Blood Fibrin, *Arch. Int. Med.* **34**:301, 1924.
- Frisch, A.: Ueber Bluteiweissuntersuchungen bei Tuberculose, *Beitr. z. Klin. d. Tuberk.* **48**:145, 1921.
- Frisch, R. A.; Mendel, L. B., and Peters, J. P.: The Production of Edema and Serum Protein Deficiency in White Rats by Low Protein Diets, *J. Biol. Chem.* **84**:167, 1929.
- Galehr, O.: Die Serumeiweisskörper bei malignen Tumoren, *Wien. Arch. f. inn. Med.* **9**:379, 1924.
- Geill, T.: Ueber den Gehalt an Albumin und Globulin im Blutserum unter normalen und pathologischen Verhältnissen, *Klin. Wchnschr.* **6**:220, 1927.  
 Kliniske undersøgelser over albumin og globulin i blodet og i urinen hos patienter med nyre-sygdomme, *Bibliot. f. læger* **120**:529, 1928.
- Georgopoulos: Experimentelle Beiträge zur Frage der Nierenwassersucht, *Ztschr. f. klin. Med.* **60**:411, 1906.
- Gilbert, A., and Chiray: Diminution des substances albumineuses du serum sanguin chez les cirrhotiques ascitiques, *Compt. rend. Soc. de biol.* **63**:487, 1907.
- Gorter, E.: Zur Pathogenese und Therapie des Mehlährschadens, *Monatschr. f. Kinderh.* **25**:211, 1923.
- Gortner, R. A.: *Outlines of Biochemistry*, New York, John Wiley & Sons, 1929.
- Govaerts, P.: Quotient albumines-globulines et pression osmotique des protéines du sérum, *Compt. rend. Soc. de biol.* **95**:724, 1926.
- Gram, H. C.: The Results of a New Method for Determining the Fibrin-Percentage in Blood and Plasma, *Acta med. Scandinav.* **56**:107, 1922.
- Grenet, H.: Diminution des albumines du sérum sanguin chez les hépatiques, *Compt. rend. Soc. de biol.* **63**:552, 1907.
- Groat, W. A., and Brewer, R. K.: Bence-Jones Protein, *J. Lab. & Clin. Med.* **1**:895, 1916.
- Gussio, S.: Sul significato biologica e sul valore diagnostico del quoziente albuminideo del siero nei cancers, *Tumori* **10**:1, 1923; abstr., *Kongresszentralbl. f. d. ges. inn. Med.* **32**:230, 1924.
- Halliburton, quoted by Starlinger and Winands.
- Hammarsten, O.: Ueber das Paraglobulin, *Arch. f. d. ges. Physiol.* **17**:413, 1878.  
 Ueber die Eiweissstoffe des Blutserums, *Ergebn. d. Physiol.* **1**:330, 1902.
- Hektoen, L., and Welker, W. H.: Further Observations on Precipitin Reaction of Bence-Jones Protein, *J. Infect. Dis.* **34**:440, 1924.
- Hellmuth, K.: Refraktometrische Eiweissbestimmung der Odemflüssigkeit bei Schwangerschaftsnierenerkrankungen und Eklampsien, *Centralbl. f. Gynäk.* **46**:290, 1922.
- Hiller, A.; Linder, G. C.; Lundsgaard, C., and van Slyke, D. D.: Fat Metabolism in Nephritis, *J. Exper. Med.* **39**:931, 1924.
- McIntosh, J. F., and van Slyke, D. D.: The Excretion of Albumin and Globulin in Nephritis, *J. Clin. Investigation* **4**:235, 1927.
- Hoffman, F. A.: Globulinbestimmungen im Ascites-Flüssigkeiten, *Arch. f. exper. Path. u. Pharmacol.* **16**:133 and 148, 1883.

- Hopkins, G. F., and Savory, H.: A Study of Bence-Jones Protein, and of the Metabolism in Three Cases of Bence-Jones Proteinuria, *J. Physiol.* **42**:189, 1911.
- Howe, P. E.: A Micro Method of Determining the Proteins in the Blood, *J. Biol. Chem.* **49**:109, 1921; *ibid.* **57**:235, 1923.
- Ikeda, K.: Personal communication to the author.
- Isaak-Krieger, K., and Hiege, A.: Der Fibrinogengehalt des Blutes bei Lebererkrankungen, *Klin. Wchnschr.* **2**:1067, 1923.
- Jacobson, V.: A Case of Multiple Myeloma with Chronic Nephritis Showing Bence-Jones Protein in the Urine and Blood Serum, *J. Urol.* **1**:167, 1917.
- Jacoby, F.: Chemische Untersuchungen am Leichenblut: Ein Beitrag zur Blutgerinnungs- und Thrombosefrage, *Virchows Arch. f. path. Anat.* **274**:292, 1929.
- von Jaksch, R.: Ueber die Zusammensetzung des Blutes gesunder und kranker Menschen, *Ztschr. f. klin. Med.* **23**:187, 1893.
- Jansen, W. H.: Die Odemkrankheit, *Deutsches Arch. f. klin. Med.* **131-132**:144, 1920.
- Jellinek, S.: Zur klinischen Diagnose und pathologischen Anatomie des multiple Myeloms, *Virchows Arch. f. path. Anat.* **177**:96, 1904.
- Jones, L. R.: Plasma Protein in Relation to Suspension Stability of Erythrocytes in Precipitation of Serum Protein with Aluminum Sulphate, *J. Lab. & Clin. Med.* **15**:209, 1929.
- Kahn, M.: The Protein and Lipin Content of Blood Serum in the Nephritides, *Arch. Int. Med.* **25**:113, 1920.
- Kapteyn, W. H. O.: Sedimentation Speed of Erythrocytes and Serum Protein Values, *Nederl. maandschr. v. geneesk.* **15**:273, 1928; *abstr.*, *J. A. M. A.* **91**:1586, 1928.
- Karger, P., and Ullmann, H.: Kasuistischer Beitrag zur Frage Ausheilung der Lipoidnephrose, *Klin. Wchnschr.* **4**:502, 1925.
- Kaufmann, J., and Mason, E.: Nephrosis, *Arch. Int. Med.* **35**:561, 1925.
- Klimesch, E., and Weltmann, O.: Beitrag zur Frage über der klinischen Wert der Fibrinogenbestimmung, *Med. Klin.* **23**:1146, 1927.
- Kohman, E. A.: War Dropsy; a Preliminary Note on the Experimental Production of Edema as Related to "War Dropsy," *Proc. Soc. Exper. Biol. & Med.* **16-17**:121, 1918-1920.
- The Experimental Production of Edema as Related to Protein Deficiency, *Am. J. Physiol.* **51**:378, 1920.
- Kollert, V.: Ueber das Wesen der Nephrosen, *Ztschr. f. klin. Med.* **97-98**:287, 1923-1924.
- and Finger, A.: Ueber die Beziehungen der Nephritis zum Cholesterin (Lipoid) Stoffwechsel, *München. med. Wchnschr.* **65**:816, 1918.
- and Starlinger, W.: Die Albuminurie als Zeichen vermehrter Eiweisserfalles bei geschädigter Nierenfunktion, *Ztschr. f. d. ges. exper. Med.* **30**:292, 1922.
- Kollmann, P.: Zur Ätiologie und Therapie der Eklampsie, *Centralbl. f. Gynäk.* **21**:341, 1897.
- Koref, O.: Klinische Analyse einer Amyloidose, *Med. Klin.* **20**:1243, 1924.
- Krausz, E.: Studien zur Bence-Jones'schen Albuminurie, *Deutsches Arch. f. klin. Med.* **137**:257, 1921.
- Lewin, G.: Die klinische Bedeutung der Globulin-Albumin Bestimmungen im Serum, *Med. Klin.* **23**:643, 1927.

- Lewinski, J.: Beobachtungen ueber den Gehalt des Blutplasms an Serumalbumin, Serumglobulin und Fibrinogen, *Arch. f. d. ges. Physiol.* **100**:611, 1903.
- Limbeck, R., and Pick, F.: Ueber die quantitativen Verhältnisse der Eiweisskörper im Blutserum von Kranken, *Prag. med. Wchnschr.* **18**:133, 149 and 165, 1893.
- Ueber die quantitativen Verhältnisse der Eiweisskörper im Blutserum von Kranken, *Deutsche med. Wchnschr.* **20**:563, 1894.
- Linder, G. C.; Lundsgaard, C.; van Slyke, D. D., and Stillman, E.: The Cause of Low Plasma Protein Concentration in Nephritis, *Proc. Soc. Exper. Biol. & Med.* **20**:319, 1923.
- Lundsgaard, C., and van Slyke, D. D.: The Concentration of Plasma Proteins in Nephritis, *J. Exper. Med.* **39**:887, 1924.
- Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis, *ibid.* **39**:921, 1924.
- Lloyd, R. B., and Paul, S. M.: Serum Changes in Kala-Azar, *Indian J. M. Research* **16**:203 and 529, 1928.
- Loebner, C.: Untersuchungen über das Blutserum bei Carcinom, *Deutsches Arch. f. klin. Med.* **127**:397, 1918.
- Loeper, M., and Tonnet: L'accroissement paradoxal des albumines du sérum de certains cancéreux, *Compt. rend. Soc. de biol.* **83**:1032, 1920.
- Löwenthal, K.: Zur Frage der Lipoidnephrose, *Virchows Arch. f. path. Anat.* **261**:109, 1926.
- McLester, J. S.: The Diagnostic Value of Blood Fibrin Determination with Special Reference to Disease of the Liver, *J. A. M. A.* **79**:17, 1922.
- Davidson, M. F., and Frazier, B.: Blood Fibrin Changes in Various Diseases, with Special Reference to Disease of the Liver, *Arch. Int. Med.* **35**:177, 1925.
- Magnus-Levy, A.: Ueber Bence-Jones'schen Eiweisskörper, *Ztschr. f. physiol. Chem.* **30**:200, 1900.
- Mason, E. H.: The Life History of a Case of Nephrosis, *Internat. Clin.* **1**:163, 1926.
- Maver, M. B.: Nutritional Edema and War Dropsy, *J. A. M. A.* **74**:934, 1920.
- Munk, F.; Benatt, A., and Flockenhaus: Experimentelle Untersuchungen über das Wesen der Albuminurie und der Lipoidnephrose, *Klin. Wchnschr.* **4**:863, 1925.
- Munk, J.: Hyperglobulinemia and hypoglobulinemia, *Nederl. maandschr. v. geneesk.* **15**:432, 1929.
- Murphy, F. D.: Chronic Glomerulonephritis with Lipoid Changes, *Arch. Int. Med.* **45**:23, 1930.
- Muschel, A.: Note on the Fractionation of Serum Proteins by Means of Ammonium Sulphate, *J. Biol. Chem.* **78**:715, 1928.
- Myers, V. C.: Chemical Changes in the Blood and Their Clinical Significance, *Physiol. Rev.* **4**:279, 1924.
- Nasse, H.: Das Blut der Schwangeren, *Arch. f. Gynäk.* **10**:315, 1876.
- Nonnenbruch: Ueber extrarenale Ödemgenese und Vorkommen von konzentriertem Blut bei hydropschen Nierenkranken, *Deutsches Arch. f. klin. Med.* **136**:170, 1921.
- Oliva, C.: Physikalisch-chemische Veränderungen des Blutes nach Aderlass und subcutaner Infusion, *Ztschr. f. klin. Med.* **73**:289, 1911.
- Ornstein, O.: Ueber den Eiweissaufbau des Serum-Globulins und dessen Beziehungen zu den Antikörpern, *Klin. Wchnschr.* **7**:1081, 1928.

- Pfeiffer, T.: Ueber den Fibringehalt des menschlichen Blutes und die Beziehungen desselben zur sogenannten Crusta phlogistica, *Ztschr. f. klin. Med.* **33**:215, 1897.
- Rabinowitch, I. M., and Childs, M. C. C.: A Contribution to the Biochemistry and Treatment of Chronic Nephrosis (Epstein), *Arch. Int. Med.* **32**:758, 1923.
- Reimann, H. A.: Kidney Function in Pneumonia, *J. Clin. Investigation* **3**:123, 1926.
- Reisz, E.: Klinische Eiweissbestimmungen mit dem Refraktometer, *Verhandl. d. 76 Versamml. deutsch. Naturforsch. u. Ärzte (Breslau)*, 1904, p. 36.
- Die refraktometrische Blut-Untersuchung und ihre Ergebnisse für die Physiologie und Pathologie des Menschen, *Ergebn. d. inn. Med. u. Kinderh.* **10**:531, 1913.
- Zur Klinik und Einteilung der Uremia, *Ztschr. f. klin. Med.* **80**:424 and 452, 1914.
- Bemerkungen zur praktischen Verwertung der Refraktometrie des Blutserums, *Deutsches Arch. f. klin. Med.* **117**:175, 1914-1915.
- Rigler, L. G., and Rypins, H.: Chronic Nephrosis, *Minnesota Med.* **7**:419, 1924.
- Robertson, T. B.: A Micro-Refractometric Method of Determining the Percentage of Globulin and Albumin in Very Small Quantities of Blood Serum, *J. Biol. Chem.* **22**:233, 1915.
- Rohrer, F.: Bestimmung des Mischungsverhältnisses von Albumin und Globulin im Blutserum, *Deutsches Arch. f. klin. Med.* **121**:221, 1916-1917.
- Rowe, A. H.: The Albumin and Globulin Content of Human Blood Serum, *Arch. Int. Med.* **18**:455, 1916.
- Refractometric Studies of Serum Proteins in Nephritis, Cardiac Decompensation, Diabetes, Anemias, and Other Chronic Diseases, *ibid.* **19**:354, 1917.
- Rusznayák, S.: Untersuchungen über die Entstehung des Ödems bei Nierenkranken, *Ztschr. f. d. ges. exper. Med.* **41**:533, 1924.
- Barát, I.; Kürthy, L.: Untersuchungen über die klinische Bedeutung der Eiweissfraktionen des Blutplasmas, *Ztschr. f. klin. Med.* **97-98**:337, 1923-1924.
- Salvesen, H. A.: Plasma Proteins in Normal Individuals, *Acta med. Scandinav.* **65**:147, 1926-1927.
- Hyperproteinemia in a Case of Nephrosis, *ibid.* **65**:152, 1926-1927.
- Sandelowsky, J.: Ueber den Einfluss die Temperatur-Steigerung auf die Blutkonzentration, *Deutsches Arch. f. klin. Med.* **100**:324, 1910.
- Schade, H., and Menschel, H.: Ueber die Gesetze der Gewelsquellung und ihre Bedeutung für klinische Fragen (Wasseraustausch im Gewebe, Lymphbildung und Ödementstehung), *Ztschr. f. klin. Med.* **96**:279, 1923.
- Scheffer, W.: Zur Frage des Fibrinogengehaltes des Blutes bei Lebererkrankungen, *Klin. Wchnschr.* **2**:1456, 1923.
- Scheurben, F.: Das Verhalten des Albumin-Globulin Verhältnisses im Serum, der Blutkörperchen-Sehnkungsgeschwindigkeit und der von Pirquetschen Hautreaktion bei Lungentuberkulose im vergleichender Betrachtung, *Beitr. z. klin. d. Tuberk.* **69**:59, 1928.
- Schindera, M.: Das Eiweissbild des Blutplasmas unter pathologischen Bedingungen, *Deutsches Arch. f. klin. Med.* **143-144**:113, 1923-1924.
- Schlayer, quoted by Kollert.
- Schlutz, F. W.; Swanson, W. W., and Ziegler, M. R.: The Distribution of the Globulin and Albumin Fractions in the Blood and Urine in Nephrosis, *Am. J. Dis. Child.* **36**:756, 1928.

- Schoch, quoted by Starlinger and Winands.
- Schwartz, H., and Kohn, J. L.: Studies of Nephritis in Children, *Am. J. Dis. Child.* **24**:125, 1922.
- Short, J. J., and Crawford, J. R.: Bence-Jones Protein in Blood Serum Leading to Detection of Multiple Myelomatosis, *J. Lab. & Clin. Med.* **14**:1092, 1929.
- Silver, H., and Lindbloom, A.: Ein Fall von allgemeiner Amyloidose ohne nachweisbare Ursache, *Acta med. Scandinav.* **64**:529, 1926.
- Simon, C. E.: Observations on the Nature of the Bence-Jones Albumin, *Am. J. M. Sc.* **123**:929, 1902.
- Stahlberg, H.: Ueber die Bedeutung der Refraktometrie bei Differentialdiagnose der Pneumonie im Kindesalter, *Monatschr. f. Kinderh.* **41**:413, 1928.
- Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19**:312, 1895.
- Starlinger, W.: Ueber das Verteilungsverhältnis der Eiweisskörpergruppen im tertiar-syphilitischen Sera bei positiver Komplementbindungsreaktion, *Biochem. Ztschr.* **169-170**:449, 1926.
- Ueber das Verhalten den zirkulierenden Eiweisskörper des menschlichen Plasmas unter normalen und krankhaften Bedingungen, *Deutsche med. Wchnschr.* **54**:731, 1928.
- and Winands, E.: Ueber das Verteilungsverhältnis der zirkulierenden Eiweisskörper im Verlauf krankhaften Zustände, *Ztschr. f. d. ges. exper. Med.* **60**:138, 160 and 185, 1928.
- Steggerda, F. R.: Some Properties of Muscle with Special Reference to Water, unpublished thesis, 1929.
- Steinbrinck, quoted by Starlinger and Winands.
- Strauss, H.: Untersuchungen über den Wassergehalt des Blutserums bei Herz- und Nierenkranken, *Ztschr. f. klin. Med.* **60**:501, 1906.
- Taylor, A. E.; Miller, C. W., and Sweet, J. E.: Studies in Bence-Jones Proteinuria, *J. Biol. Chem.* **29**:425, 1917.
- Miller, C. W., and Sweet, J. E.: Studies in Bence-Jones Proteinuria. *J. Biol. Chem.* **29**:425, 1917.
- Thannhauser, S. J., and Krausz, E.: Ueber eine degenerative Erkrankung der Harnkanälchen (Nephrose) bei Bence-Jones'scher Albuminurie mit Nierenschwund (Kleine, Glatte, Weisse, Niere), *Deutsches Arch. f. klin. Med.* **133**:183, 1920.
- Thomas, T. A., and Andrews, E.: A New Clinical Test for Tissue Thirst, *Arch. Int. Med.* **42**:776, 1928.
- Tranter, C. J., and Rowe, A. H.: The Refractometric Determination of Albumin, Globulin, and Nonprotein, *J. A. M. A.* **65**:1433, 1915.
- Vandorfy, J.: Ein mit Pneumococcusperitonitis verlaufender Fall von Nephrose, *Med. Klin.* **17**:656, 1921.
- Veil, W. H.: Ueber die klinische Bedeutung der Blutkonzentrationsbestimmung, *Deutsches Arch. f. klin. Med.* **113**:226, 1913-1914.
- Verney, E. B.: The Osmotic Pressure of the Proteins of Human Serum and Plasma, *J. Physiol.* **61**:319, 1926.
- Volhard, F.: Ueber Wesen und Behandlung der Brightschen Nierenkrankheiten, *Deutsche med. Wchnschr.* **44**:393, 1918.
- Weber, F. P.; Hutchinson, R., and Macleod, J. J. R.: Multiple Myeloma (Myelomatosis) with Bence-Jones Protein in the Urine, *Am. J. M. Sc.* **126**:644, 1913.

- Weltmann, O., and Neumayer, K.: Das Fibrinogen im diagnostischen Kalkul der Leberkrankheiten, *Med. Klin.* **21**:629, 1925.
- Wichert, M., and Ruszjajewa-Oparina, A.: Klinische Beobachtungen bei Cholesterinämie und Bilirubinämie, *Ztschr. f. klin. Med.* **101**:185, 1924.
- Winternitz, R.: Ein Beitrag zur chemischen Untersuchung des Blutes rezent luetischer Menschen, *Arch. f. Dermat. u. Syph.* **93**:65, 1908.
- Ein weiterer Beitrag zur chemischen Untersuchung des Blutes rezent luetischer Menschen, *ibid.* **98-99**:441, 1909.
- Zweiter Beitrag zur chemischen Untersuchung des Blutes rezent luetischer Menschen, *ibid.* **100-101**:227, 1910.
- Zangemeister, W.: Die Eklampsie eine Hirndruckfolge, *Ztschr. f. Geburtsh.* **79**:124, 1916-1917.
- Der Hydrops gravidarum, sein Verlauf und seine Beziehungen zur Nephropathie und Eklampsie, *ibid.* **81**:491, 1919.

## STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

### IX. DEPOSITION OF CALCIUM IN BONE IN HEALING SCORBUTUS\*

WILLIAM T. SALTER, M.D.

AND

JOSEPH C. AUB, M.D.

BOSTON

In studying calcium metabolism, and particularly the storage of calcium within bone, Bauer, Aub and Albright<sup>1</sup> pointed out that the spicules along the medullary canal and in the cancellous portion of the ends of long bones were markedly resorbed in animals fed a diet low in calcium. They demonstrated that after the receipt of a diet high in calcium new bone was laid down only in the trabeculae. This was partly determined by the use of alizarin red, which stains only newly formed bone deep red. In order to determine the site of repair in general metabolic disturbances which affect bone, the dye has been again used to mark newly deposited calcium. In view of the slow progress of the metabolism of bone it was expedient to study a process which would produce a rapid change in bone, so that confusion with slow alterations in normal deposit of calcium might be avoided. Such rapid variations occurred in the work of Wolbach and Howe,<sup>2</sup> who showed that guinea-pigs became scorbutic in about two weeks when they were fed diets deficient in vitamin C. We have used their work as a means of studying the site of loss of calcium from the bones from other than physiologic causes.

#### METHODS

Young adult guinea-pigs, each weighing about 500 Gm., were housed in cages containing a very small amount of sawdust. They were fed the scorbutus-producing diet described by Wolbach and Howe, with shreds of filter paper for roughage. Usually during the third week the animals began to show a disturbance of the joints by their quietness and stiff gait. During the fourth week they ate poorly, and shortly thereafter died, unless given orange juice.

Sodium alizarin sulphonate was used in a saturated solution (nearly 2 per cent) in physiologic solution of sodium chloride. The injection of 0.5 cc. of this intra-

\* Submitted for publication, June 19, 1930.

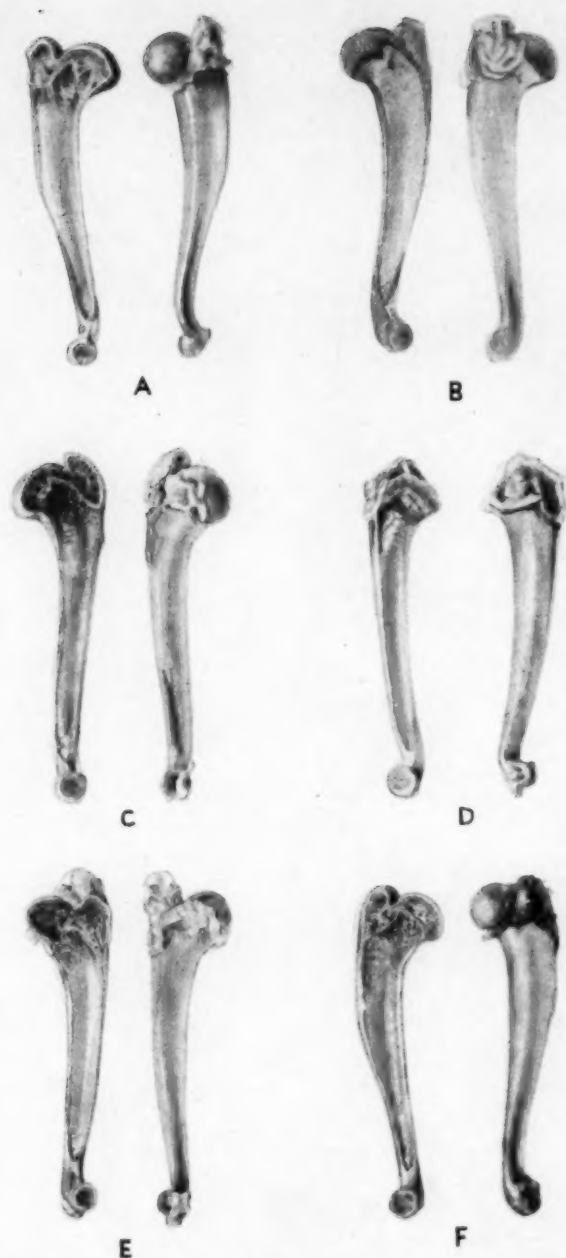
\* From the Medical Clinic of the Massachusetts General Hospital.

\* Aided financially in part by the Lead Fund of the Harvard School of Public Health.

\* Miss Frances M. Angier prepared the diet.

1. Bauer; Aub, and Albright: A Study of the Bone Trabeculae as a Readily Available Reserve Supply of Calcium, *J. Exper. Med.* **49**:145, 1929.

2. Wolbach and Howe: Intercellular Substances in Experimental Scorbutus, *Arch. Path.* **1**:1, 1926.



The influence of orange juice on the deposit of calcium in guinea-pigs maintained on a diet otherwise deficient in Vitamin C.

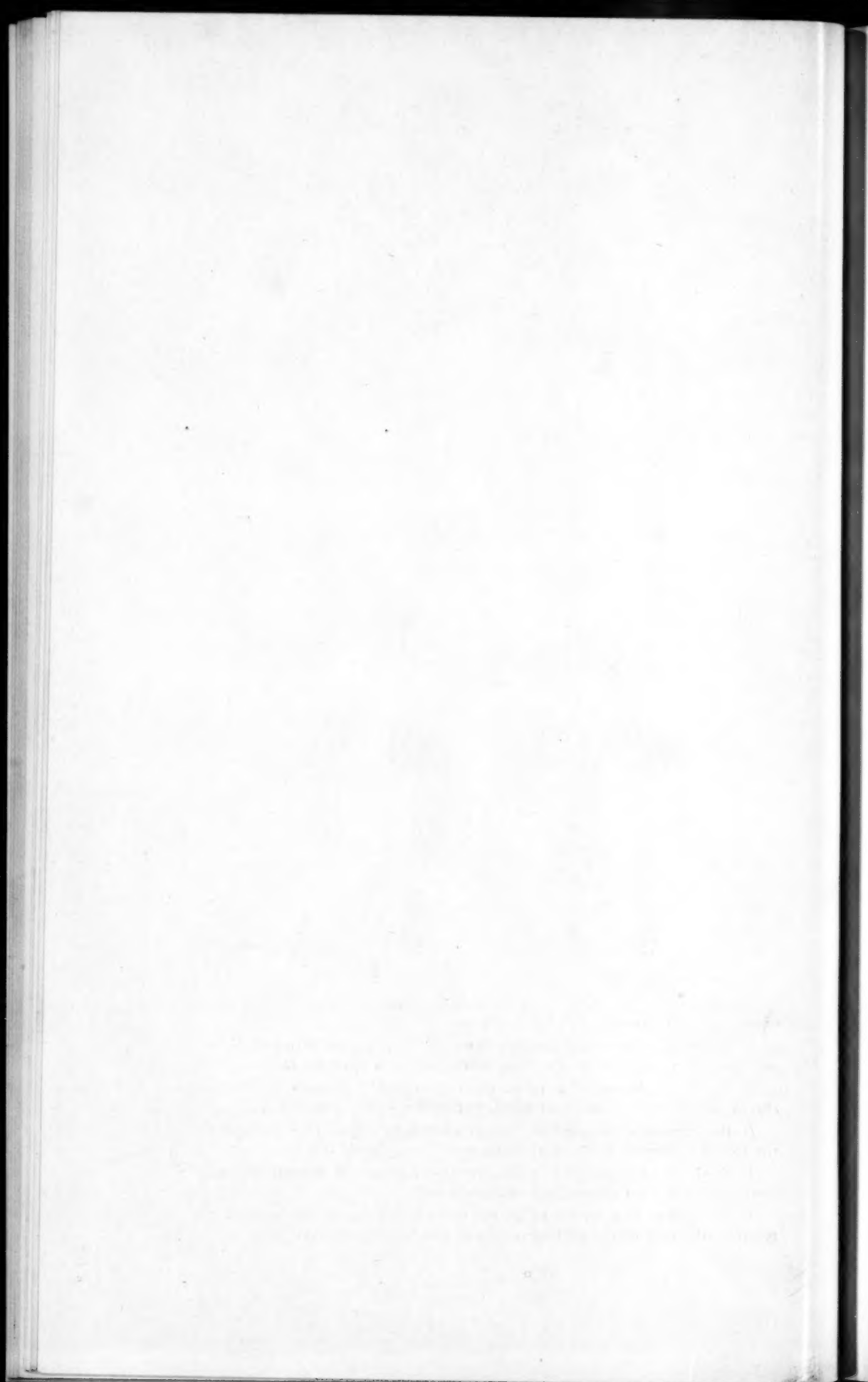
*A*, the humerus from a guinea-pig that received both orange juice and alizarin red from the twenty-first to the thirty-fourth day of a scorbutic diet.

*B* and *C*, the humeri of a guinea-pig that received both orange juice and alizarin red from the thirtieth to the forty-first day of a scorbutic diet.

*D*, the humerus of a guinea-pig that received both orange juice and alizarin red from the thirtieth to the forty-fourth day of a scorbutic diet.

*E*, the humerus of a control guinea-pig that died on the thirtieth day of a scorbutic diet without orange juice or alizarin red.

*F*, the humerus of a control guinea-pig that received orange juice and alizarin red from the start of the scorbutic diet, and was killed after seven weeks.



peritoneally usually proves toxic and may indeed kill the guinea-pig. Most of our injections therefore were given intramuscularly in the gluteal region twice a week.

The humerus was selected as the bone for investigation in this series. It was split by means of the circular mechanical dental saw recommended by Howe, and the two halves of the bone were digested in a mixture of pancreatic trypsin and bile or in duodenal contents, buffered at  $pH$  8. The final cleaned specimen was preserved in an alkaline formaldehyde (10 per cent) solution.

Unless the organic matter is completely removed, there remains behind a dirty-brown discoloration of the bone, which may obscure the color of the alizarin; occasionally hemoglobin persisting in a freshly split bone may simulate this color, especially when fresh periosteal hemorrhages have been present. For this reason bones of scorbutic animals that had received no dye were used to control the technic of digestion. These bones were nearly ivory white. It was at first intended to follow the same experimental procedure used by Bauer, Aub and Albright, in which a foreleg was amputated as a control of the changes in the contralateral bone. The scorbutic animals ate so poorly after operation, however, that this method of procedure was finally abandoned, and control animals were relied on to check the experiment.

The effect of the injection of alizarin blue black B also was tried on growing rats and kittens, and on the teeth of adult rodents (rats and guinea-pigs). Injections of the blue dye were made at weekly intervals for from six to eight weeks, and the animals, watched for many months, were killed at occasional intervals. Although control animals that had received injections of alizarin red showed reddening of the teeth or bone, there was no evidence of deposition of the blue color in the teeth or in growing bone; the retroperitoneal lymph nodes and lymphatic channels, however, were filled therewith.

As the actual amount of new bone laid down during the few weeks of the experiments on guinea-pigs was much smaller than in the case of a fracture-callus<sup>3</sup> or even of new spicules laid down under prolonged feeding of diets of high calcium content, care had to be taken not to remove mechanically or chemically a thin, bony external film containing alizarin. Some of the tissue was osteoid in consistency, and as it digested out left small fragments of better calcified tissue unsupported or only poorly adherent. The color change, too, was not so striking as in the experiments mentioned earlier, in which more calcium was deposited.

#### COMMENT ON THE RESULTS

The accompanying figure indicates the sites of the deposition of alizarin in the bones of animals used in typical experiments. The distribution of dyestuff in the humerus followed the classic description of scorbutic lesions. The epiphyseal line was particularly well marked; this was seen both externally and within the split bone. The cancellous tissue of the epiphysis and diaphysis was stained, and pink spicules extended a short way into the medullary cavity. Externally, the shaft near the head distal to the epiphyseal line was usually stained for a variable, but considerable, distance, and frequently a large patch of red was found along the distal portion of the body of the bone, suggesting this as the site of a previous subperiosteal hemorrhage. There was

3. Brooks, Barney: Studies in Regeneration and Growth of Bone, *Ann. Surg.* 65:704, 1917; Studies in Bone Regeneration, *Ann. Surg.* 66:625, 1917.

greater involvement of the trabecular portions of the bone as contrasted with the shaft.

The bones of control animals receiving no orange juice or receiving orange juice from the commencement of the diet showed no deposition of alizarin. Some control animals receiving alizarin during the production of scurvy showed at death slight reddening of the exterior of the bone, but no dye in the trabeculae. In one successful operative experiment, in which a fore limb was amputated after twenty-eight days of the scorbutic diet (two weeks after abortion), no appreciable amount of dye was detected, although injections of alizarin had been proceeding for three weeks. The contralateral leg, after five weeks' feeding of orange juice, showed reddening of both spicules and the external shaft. These control experiments indicated little or no deposition of calcium during acute experimental scorbutus.

The specimens indicated macroscopically the extent to which the healing of acute scorbutus may precipitate new formation of bone. The experiments of Wolbach and Howe indicated that the healing process in scorbutus involves the setting of a material already present. It was by no means certain, therefore, that alizarin would be deposited in such a matrix when it solidified with the deposition of calcium salts. Our observations show that newly deposited lime salts produced by the healing of a metabolic disease may be marked by alizarin red just as is newly formed bone in other processes not connected with vitamin deficiency. György<sup>4</sup> has just published roentgenologic evidence following overdosing with viosterol, corresponding to these results.

It is evident that the supply of vitamin may rapidly affect the deposition of calcium within the trabeculae, and that the reserve store of calcium is influenced by the vitamin, as well as by the calcium of the diet and the parathyroid hormone. It is probable, however, that the mechanism is quite different, for with the deficiency in vitamin it is the underlying cellular structure<sup>5</sup> that is primarily at fault.

#### SUMMARY

Calcium fails to be deposited in bone when the diet, though adequate in calcium, is deficient in vitamin C. The subsequent addition of vitamin C to such a diet allows calcium to be rapidly deposited.

This deposit is largely at the epiphyseal ends of the bone and in the trabeculae. In other words, not only growth, but also the stores of the reserve supply of calcium are involved by the pathologic changes in the bone cells.

4. György, P.: Die besondere Stellung der subepiphysären Knochenschicht im Kalkstoffwechsel als eines leicht mobilisierbaren Kalkspeichers, *Klin. Wchnschr.* 9:102, 1930.

5. Wolbach and Howe (footnote 2).

## PARADOXICAL EMBOLISM \*

L. R. FRENCH

BALTIMORE

The chance of seeing a thrombus pass through the foramen ovale is so rare that the following case is worthy of note.

A woman, aged 36, died twenty-nine days after hysteromyomectomy and after having shown various clinical evidences of embolic occlusion of branches of the pulmonary artery. At autopsy, an old embolus was found completely obstructing the branch of the right pulmonary artery leading to the lower lobe and partially blocking the middle and upper branches. The time of its lodgment was apparently indicated by an abrupt rise in temperature and pulse rate, with a pain in the lower part of the right side of the chest on the sixth day after operation. A partially organized embolus filled the entire left pulmonary artery, and its arrival was marked by a sudden rise in the pulse rate on the twenty-fourth day. A third fresh embolus occluded the remaining upper branches of the right pulmonary artery and had lodged there at the time of the last acute clinical symptoms fifteen minutes before death.

The heart showed a long thrombus caught half way through the foramen ovale, so that part hung in the right auricle and the rest in the left (figs. 1 and 2). From its form, it had evidently been molded in a vein, but so many large emboli had already been dislodged that it is impossible to be sure of its point of origin. The great obstruction of the pulmonary circulation, which has been observed in about half of the cases of this sort already reported, must have increased the blood pressure in the right side of the heart and caused its dilatation, decreasing the pressure in the left auricle, a condition thought to favor paradoxical embolism. This must also have favored the twisting and turning of the embolus, which finally penetrated the foramen ovale, while still in the right auricle, for it was the distal end of the mold of the vein that had passed into the left auricle.

The embolus was 16 cm. long and in the form of a tapering cylinder. The part which still hung in the right auricle was 1 cm. thick and grayish. About 1 cm. of it remained in the right auricle, its end dividing into two short branches—broken stumps evidently formerly continuous with another portion that may have been dislodged previously. In the left auricle, the rest of the embolus hung down 5 cm., passing through the mitral ring to a point 0.5 cm. below the margin of the leaflets. There it folded back on itself for nearly 4 cm., terminating in a second U-shaped fold in the left auricle. This terminal part measured only 4 mm. in thickness and was dark red.

No special symptoms could be expected from this plugging of the foramen ovale, and it is evident that there was no time for the embolus to be broken and thrown in fragments into the systemic arterial circulation. No evidence of embolism of arteries in other organs was found.

---

\* Submitted for publication, Sept. 16, 1930.

\* From the Department of Pathology of Johns Hopkins University.



Fig. 1.—Right auricle. Remainder of embolus projecting from the foramen ovale.



Fig. 2.—Left side of the heart. Embolus hanging from foramen ovale and down through the mitral orifice.

# PRIMARY NEOPLASMS OF THE PLEURA

A REPORT OF FIVE CASES \*

PAUL KLEMPERER, M.D.

AND

COLEMAN B. RABIN, M.D.

NEW YORK

Although primary pleural neoplasms are classed among the rarer types of tumors, their importance has been recognized in a rather extensive literature. Their histogenesis and their classification are still subjects of controversy. A study of the entire group of pleural tumors permits a classification which appears to be of value, not only theoretically, but also from a practical standpoint, for the recent advancement in thoracic surgery has made the successful removal of some of these growths possible.

Macroscopically, the tumors may be sharply divided into two main groups. The first consists of those primarily localized in one part of the pleura. The second consists of those of a diffuse nature, involving the entire pleura and usually ensheathing the lung in tumor tissue. The latter group is mainly of academic interest; it forms the subject of the second part of this paper.

## LOCALIZED TUMORS OF THE PLEURA

Localized tumors of the pleura may involve the parietal or the visceral layer. They comprise many histologic types and benign and malignant forms. The entire group is possessed of a common characteristic: they originate from the tissues beneath the superficial lining cells, in contradistinction to the diffuse form of pleural tumors, which probably arise from the surface lining.

Tumors arising from beneath the parietal pleura of the wall of the chest vary greatly in their histologic structure because of the number of different structures that are present in this region in addition to the subserous areolar tissue. The fascia of the intercostal muscles, the nerve sheaths and the subpleural fat may also be the origin of a localized neoplasm. Malignant connective tissue tumors in this location have been described by Blumenau,<sup>1</sup> Leube,<sup>2</sup> Israel-Rosenthal (second case),<sup>3</sup>

\* Submitted for publication, Sept. 19, 1930.

\* From the Laboratories of Mount Sinai Hospital.

1. Blumenau, M. B.: Primäres Sarkom der Pleura, *Deutsche med. Wchnschr.* **22**:570, 1896.

2. Leube, W.: *Spezielle Diagnose der inneren Krankheiten*, Leipzig, F. C. W. Vogel, 1891, vol. 1, p. 166.

3. Israel-Rosenthal: Beitrag zur Klinik der primären Pleura Sarkome, *Nord. med. Ark.*, 1900, vol. 7; cited in *Virchows Jahresbericht* **352**:266, 1900.

Kaufmann<sup>4</sup> and Hofmokl.<sup>5</sup> They were all large. In Hofmokl's case, the neoplasm weighed 7 pounds (3.2 Kg.). The tumors were described as round cell sarcoma, spindle cell sarcoma and angiosarcoma. They invaded the wall of the chest and metastasized to the visceral pleura, to the mediastinal lymph nodes and occasionally to the abdominal organs. Pallasse and Roubier (case 1<sup>6</sup>) reported a lipomyxosarcoma originating from the subpleural fat over the diaphragm, and Barbier and Molland<sup>7</sup> described a malignant fatty tumor arising from beneath the mediastinal pleura. Jacobaeus and Key<sup>8</sup> and Sabrazes and Muratet<sup>9</sup> reported similar tumors originating from the fat tissue beneath the wall of the chest. Benign connective tissue tumors in this location were described by Jacobaeus and Key (cases 2, 3 and 4).<sup>8</sup> Neurosarcomas originating from the intercostal nerves were first described by Grawitz,<sup>10</sup> who mentioned five cases from his experience. In one of these cases metastases developed. Banse,<sup>11</sup> Kobilinsky<sup>12</sup> and Schmidt (second case)<sup>13</sup> described similar cases. Stewart and Adami<sup>14</sup> described a sarcoma beneath the costal pleura in which the intercostohumeral nerve was embedded. The tumor was encapsulated, but had eroded the cartilages of the ribs.

On the other hand, the tumors reported arising from the subserous layers of the visceral pleura were generally not of an invasive character. A number of small growths, fibromas, leiomyomas, lipomas and chon-

---

4. Kaufmann, E.: *Spezielle pathologische Anatomie*, Berlin, W. de Gruyter & Company, 1922, vol. 1, p. 385.

5. Hofmokl: *Endothelsarkom der rechten Pleura*, Arch. f. Kinderh. **7**:81, 1885.

6. Pallasse, E., and Roubier, C.: *Les tumeurs primitives de la plèvre*, Ann. de méd. **3**:243, 1916.

7. Barbier, J., and Molland, H.: *Un cas de tumeur maligne médiastins pleurale avec l'aspect histologique de lipo-sarcome*, Lyon méd. **138**:623, 1926.

8. Jacobaeus, H. C., and Key, E.: *Some Experiences with Intrathoracic Tumors, Their Diagnosis and Their Operative Treatment*, Acta chir. Scandinav. **53**:573, 1920-1921.

9. Sabrazes, J., and Muratet, L.: *Myxome lipomateux, intra-thoracique*, Arch. de méd. exper. et d'anat. path. **21**:580, 1909.

10. Grawitz, P.: *Demonstration einer neuen Gruppe intrathorakaler Tumoren*, Deutsche med. Wchnschr. **34**:1123, 1908.

11. Banse: *Ueber intrathoracische Fibrome, Neurome und Fibrosarkome*, Inaug. Diss., Greifswald, 1908.

12. Kobilinsky: *Ueber primäre Sarkome in der Lunge*, Inaug. Diss., Greifswald, 1904.

13. Schmidt, W.: *Ueber Fibrome der Lungenpleura*, Inaug. Diss., Greifswald, 1903.

14. Stewart, J., and Adami, J. G.: *Case of Primary Angiosarcoma of Upper Portion of Left Pleura*, Montreal M. J. **22**:1909, 1893-1894.

dromas in this location, found accidentally at postmortem examination, have been described in the literature. They will not be discussed in this paper.

By far the most interesting and important group of localized subpleural connective tissue neoplasms consists of the so-called giant sarcomas of the visceral pleura. Their pathologic interest lies in the fact that the tumors described in the literature did not metastasize or infiltrate, in spite of the microscopic picture of sarcoma. Clinically, they are of importance because, if diagnosed early enough, they may be removed, and because, if neglected, they cause death from disturbances in circulation due to the extreme proportions to which they grow.

Sixteen cases corresponding to this type have been described in the literature by: Dorendorf,<sup>15</sup> Schneider,<sup>16</sup> Mehrdorf,<sup>17</sup> Braun,<sup>18</sup> Kaufmann,<sup>4</sup> Nevinney,<sup>19</sup> Ricard,<sup>20</sup> Quincke and Garre,<sup>21</sup> Henke,<sup>22</sup> Israel-Rosenthal (case 1),<sup>3</sup> Kidd and Habershon,<sup>23</sup> Schmidt (case 1),<sup>13</sup> Kahler and Eppinger,<sup>24</sup> Podack (case 3),<sup>25</sup> Sala<sup>26</sup> and Pallasse and Roubier (cases 2 and 3).<sup>6</sup>

The tumors reported evidently grew very slowly and were present for many years before they gave rise to symptoms. By this time they were very large. The larger ones, in each case, practically filled one side of the thoracic cavity, displacing the heart and compressing the

15. Dorendorf, H.: Demonstration einer grossen Pleuratumors, *Deutsche med. Wchnschr.* **40**:225, 1914.

16. Schneider, J.: Ein anatomisch und klinisch umschriebener Typus des Pleurasarkoms, *Virchows Arch. f. path. Anat.* **252**:706, 1924.

17. Mehrdorf, R.: Fibrosarcoma myxomatoides pleurae permagnum, Beitrag zur Kenntnis der primären Pleuratumoren, *Virchows Arch. f. path. Anat.* **193**:92, 1908.

18. Braun, H.: Demonstration eines Tumors der Pleura, *Verhandl. d. deutsch. Gesellsch.* **37**:162, 1908.

19. Nevinney, H.: Beitrag zur Casuistik der "Expansiv wachsenden Pleurariesensarkome," *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **40**:277, 1927-1928.

20. Ricard, M.: Volumineux sarcome intra-thoracique d'origine pleurale, *Bull. et mém. Soc. de chir. de Paris* **34**:804, 1908.

21. Quincke and Garre: *Lungenchirurgie*, ed. 2, Jena, Gustav Fischer, 1912, p. 193.

22. Henke, F.: *Mikroskopische Geschwulstdiagnostik*, Jena, Gustav Fischer, 1906, p. 238.

23. Kidd, P., and Habershon, S. H.: Primary Myxo-Sarcoma of the Pleura, *Tr. Path. Soc. London* **49**:15, 1898.

24. Kahler, O., and Eppinger, H.: Ein Fall von intrathoracischem Tumor, *Prag. med. Wchnschr.* **7**:242, 1882.

25. Podack, M.: Zur Kenntnis des sogenannten Endothelkrebs der Pleura, *Deutsches Arch. f. klin. Med.* **63**:1, 1899.

26. Sala, A. M.: Large Fibrosarcoma (?) in the Pleura, *Arch. Path.* **9**:950, 1930.

lung. Death resulted from cardiac failure because of obstruction to the pulmonary circulation. This was evidenced by the enlargement of the right ventricle (Kahler and Eppinger,<sup>24</sup> Podack<sup>25</sup> and Nevinney<sup>19</sup>) and atherosclerosis of the pulmonary artery (Podack<sup>25</sup>).

The smaller tumors (Schneider,<sup>16</sup> Garre<sup>21</sup>) were irregular, rounded, lobulated growths, firm in consistency and gray with green and red mottlings due to degeneration and hemorrhage.

The tumors, in each case, were enclosed in a connective tissue capsule which was covered by a smooth membrane continuous with the visceral pleura. The tumors were pedunculated, and they often became secondarily adherent to the diaphragm, the costal pleura, the pericardium or other lobes of the lung. The connections between the tumor and the points of origin, as well as the points of adhesion, were usually small bands. Whereas this made for ease of removal, it often made difficult the determination of the exact point of origin. Thus Dorendorf,<sup>15</sup> Schneider<sup>16</sup> and Pallasse and Roubier<sup>6</sup> believed that in their cases the origin was from the pleura over the diaphragm.

The microscopic picture, usually that of a fibrosarcoma, varied somewhat in different cases. The case of Kahler and Eppinger<sup>24</sup> was that of a simple fibroma. Most of the others were described as spindle cell sarcoma with areas less cellular resembling fibroma and areas simulating round cell sarcoma. Kidd and Habershon,<sup>23</sup> Mehrdorf<sup>17</sup> and Israel-Rosenthal<sup>3</sup> reported myxomatous changes in their cases, and Schneider<sup>16</sup> reported the finding of giant cells. In general the picture was that of fibrosarcoma, growing to large proportions with no evidence of metastasis. In Nevinney's<sup>19</sup> case there was some infiltration of the capsule by spindle cells at the attachment of the tumor to the lung. In spite of this fact, Nevinney believed that it should not be classed with the malignant type of tumors.

In examining the available data, one comes to the conclusion that this view is justified. Whereas it is true that the duration of symptoms before death (as reported in the literature) is relatively short, the size of the tumors, the lack of metastases and the perfect encapsulation speak against malignancy. Evidence of the slowness of growth of what eventually become giant pleural tumors was presented by Wessler and Jaches<sup>27</sup> in their roentgen studies. One of us has been able to observe clinically the slow growth of three tumors, which, in all probability, are of a similar nature and which will be the subject of a future communication.

Four cases of giant tumors originating from the subserous layer of the visceral pleura have come under our observation.

27. Wessler, H., and Jaches, L.: *Clinical Roentgenology of the Chest*, Troy, N. Y., The Southworth Company, 1923, p. 296.

REPORT OF CASES<sup>28</sup>

CASE 1.—*History*.—F. I., a white woman, aged 48, had a slight cough for a number of years, to which, however, she paid little attention. Because of clubbing of her fingers, roentgenograms of the chest were made at the request of her physician, preliminary to the performance of a gynecologic operation. They showed a round shadow in the left side of the chest, measuring about 15 cm. in diameter. A thoracotomy was performed by Dr. Howard Lilienthal, and a tumor was found situated in the anterior portion of the left side of the chest, connected with the lung by broad bands and loosely adherent to the wall of the chest and to the pericardium. It was completely removed.

*Macroscopic Examination of Tumor*.—The specimen received in the laboratory was a round, irregular, nodular tumor, grayish-pink, and measuring 16 by 15 by 7 cm. (fig. 1A). On the mesial surface there projected a large oval node measuring 9 by 5 by 4 cm., which was demarcated from the main tumor by a deep incisure. The entire tumor was surrounded by a smooth, transparent capsule, which contained many blood vessels. There were numerous short fibrous bands on the flat anterior surface. To the upper anterior border there was attached a wedge-shaped piece of flattened lung tissue, the pleura of which was continuous with the capsule of the tumor. The main tumor was very firm, lobulated on section, with whitish streaks, resembling a fibroid tumor. The nodular appendage was softer, and on section it was pink, fleshy and of homogeneous structure, with a few yellow areas of necrosis.

*Microscopic Examination*.—Under low power magnification (fig. 1B), the tumor appeared to consist of rows and nests of cells, which were separated by strands of dense connective tissue. The stroma, which in places was very poor in cells, contained narrow, thin-walled blood vessels, some of which were filled with platelet thrombi. In these regions there were occasional extensive areas of necrosis.

Under higher magnification, the cells appeared uniformly spindle-shaped, with scanty, occasionally branching, cytoplasm and large oval nuclei. The nuclei were poor in chromatin and contained small angular or rounded nucleoli. Mitoses were not seen. Between the cells, which morphologically had the characteristics of fibroblasts, there were many fibers that stained red with the van Gieson stain. These fibers stood in close relationship to the fibroblasts, to which they were in part closely attached and with the protoplasmic processes of which they were in places continuous. The picture of the tumor varied in different portions according to the richness in intercellular fibers. Some parts were more and some less cellular.

Sections from the periphery of the tumor showed it to be surrounded by an acellular fibrous capsule, which was continuous with the pleura over the adjacent lung tissue. The capsule was almost entirely demarcated from the tumor. In a few places, however, it was infiltrated by tumor cells.

The uniformity of the cellular architecture with rows of fibroblasts showing remarkably little variation and the absence of mitoses, together with the macroscopic picture of an expanding growth, would have led to the diagnosis of cellular fibroma. Since, however, there was seen

28. Dr. Howard Lilienthal contributed the clinical data of cases 1 and 2, and gave permission for their inclusion in our report.

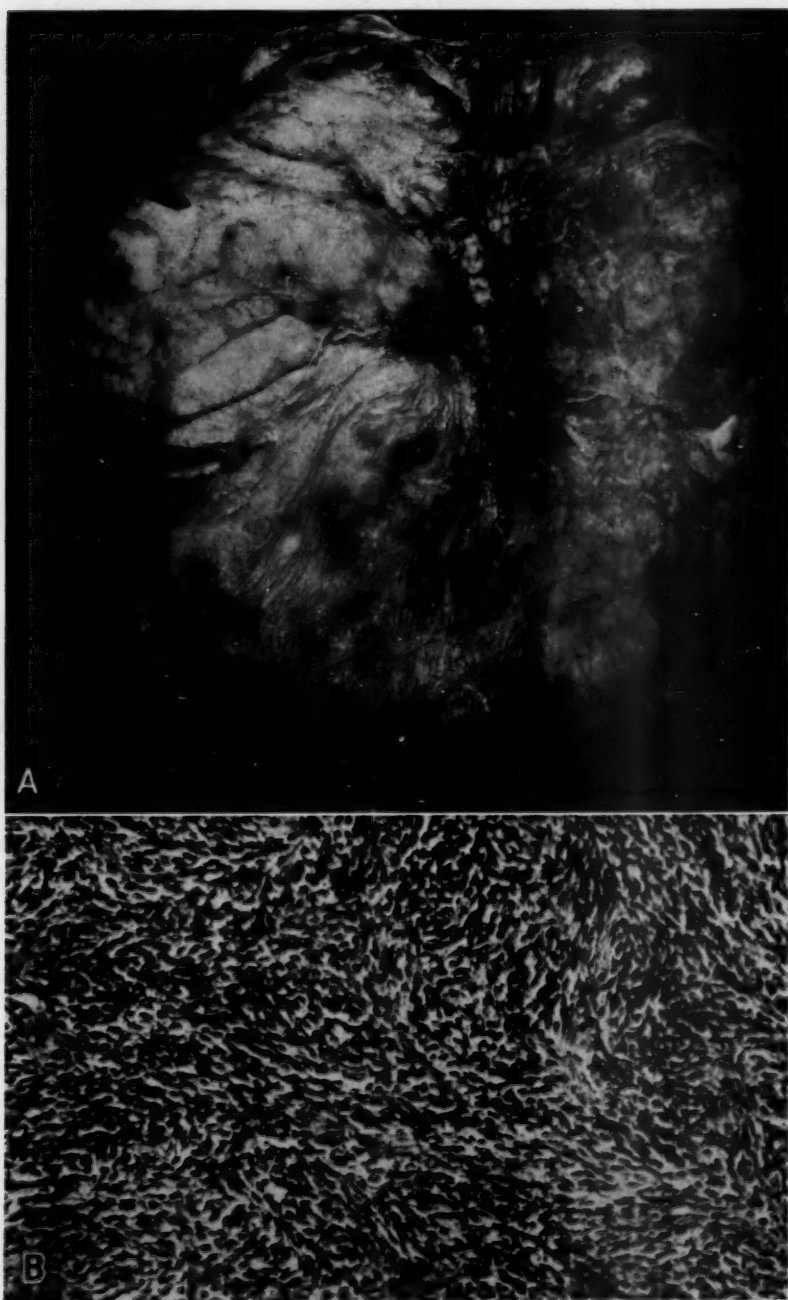


Fig. 1 (case 1).—*A*, lobular tumor showing lung attached to its superior mesial border; *B*, histologic structure of tumor.

microscopically an infiltrative growth of tumor cells in the capsule in a few places, the tumor had to be designated a fibrosarcoma. With further consideration of the clinical condition and the microscopic observations it was felt that a good prognosis could be given, especially since the tumor had been completely removed.

**CASE 2.—History.**—J. B., a man, 53 years of age, was admitted to Mount Sinai Hospital in November, 1926. He had complained of pain in the left side of the chest for a period of three years. Roentgen examination disclosed a large shadow in the left side of the chest, which was considered to be that of a neoplasm. Operation was performed by Dr. H. Lilienthal on Nov. 23, 1926. The pleural cavity was found to be obliterated by firm adhesions. Beneath the pleura there was a large, hard, whitish-gray, dense, fixed mass. Because of the extensive adhesions this could not be removed; however, a portion about the size of a tennis ball was enucleated. Microscopic examination of a section of this material by Dr. F. S. Mandlebaum showed the typical picture of fibrosarcoma. Further tissue removed a short time thereafter was examined at Roosevelt Hospital and fibrosarcoma with a low degree of malignancy was diagnosed. The patient was treated with deep irradiation.

In April, 1930, he was readmitted to Mount Sinai Hospital because of increasing symptoms in the left side of the chest. Again numerous particles of neoplasm were removed by Dr. H. Lilienthal. Roentgen examination of the right side of the chest revealed two sharply circumscribed masses in the right lung.

**Microscopic Examination of Tumor.**—Sections of the tumor removed in November, 1926, showed (fig. 2A) cellular portions composed of spindle cells with a considerable amount of intercellular collagen fibers, and other portions in which the cells were scanty, the fibers forming the bulk of the growth. The tumor cells were uniform in size and shape, and no mitotic figures were found. The diagnosis was fibrosarcoma of a low grade of malignancy.

The specimen received in the laboratory in April, 1930, consisted of several irregular masses of tissue, the aggregate material measuring about 7 by 8 by 5 mm. The portions varied considerably in consistency. Some were soft and rubbery; others were very firm. The former had a yellowish-orange, mottled appearance. On section, they presented a smooth, glistening, homogeneous surface. The central portions showed small areas of necrosis. In places they had a translucent myxomatous appearance. The firm portions of the tumor were grayish white and on section were very dense and fibrous.

Sections of the different portions of the tumor removed at operation showed a varied appearance. The very firm portions were formed by connective tissue unusually poor in cells, together with scattered, thin-walled blood vessels. The few cellular elements contained long, spindle-shaped nuclei. The softer portions of the tumor (fig. 2B) were composed of a very cellular tissue, consisting mostly of large spindle cells with oval nuclei containing a moderate amount of chromatin. Among these there were also strikingly large cells, with dark, bizarre nuclei, and giant cells with several paler nuclei. Between the cells there was a network of rather thick connective tissue fibers, which in places were collected in condensed areas that contained few cells.

Furthermore, there were portions (fig. 2C) in which there was developed a delicate, light blue ground substance between the cells. The tumor cells in these regions often showed stellate form, with long, drawn out cytoplasmic processes.

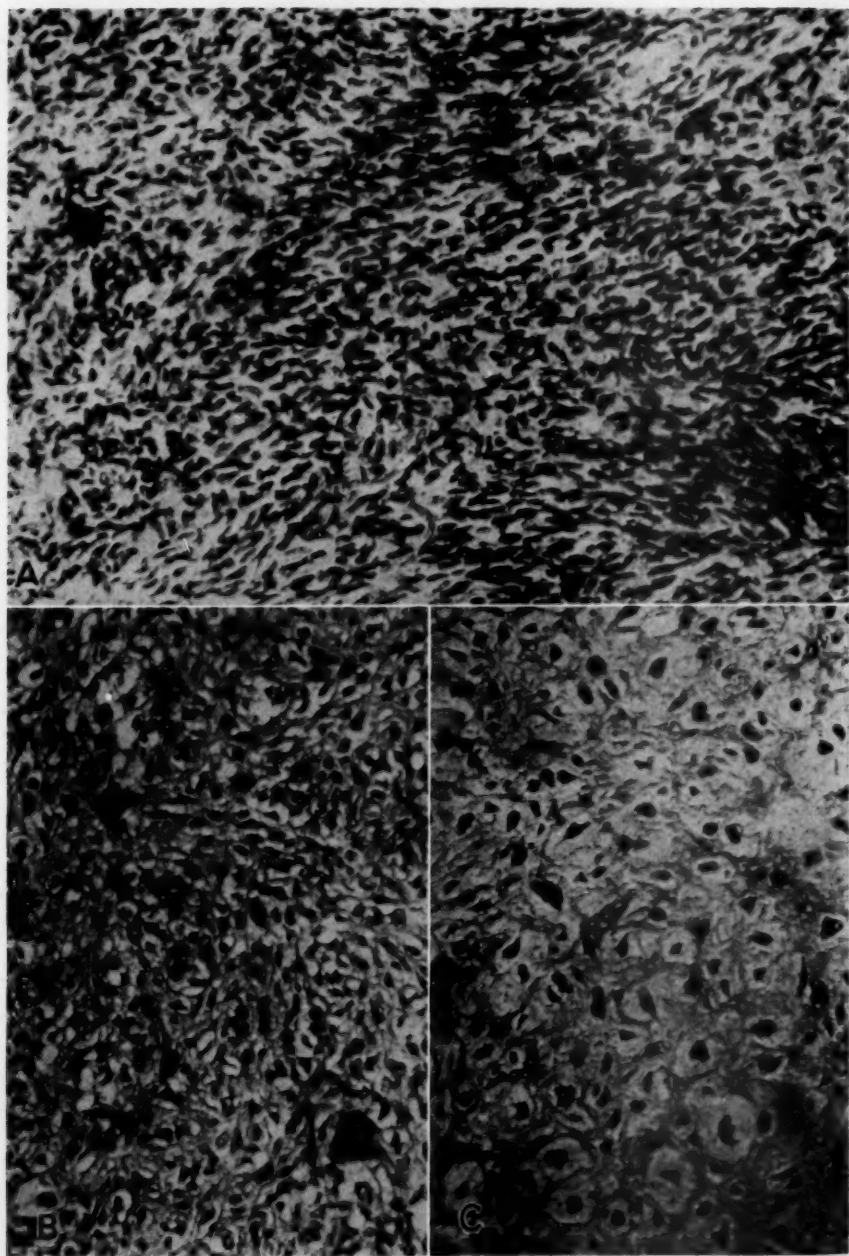


Fig. 2 (case 2).—*A*, specimen removed in 1926, representing a fibroblastic sarcoma showing uniformity of cellular structure; *B*, specimen removed in 1930, containing this area showing irregularity of cells and tumor giant cells; *C*, same as *B*, showing an area of myxosarcoma.

There was a considerable number of mitotic figures in the cellular portions of the tumor. In the periphery of the tumor there were several areas of necrosis of the tumor tissue.

*Diagnosis.*—The diagnosis was polymorphous spindle cell sarcoma with areas of myxosarcoma.

*CASE 3.—History.*—G. E., a woman, aged 50, a housewife, was admitted to the hospital on March 7, 1929. She had been admitted the first time on March 21, 1919, with a history of cough, expectoration and dyspnea of twelve years' duration. For three years, she had noticed occasional blood-tinged sputum. For two months, she had complained of epigastric distress and a striking beneath the sternum. Her condition was diagnosed as aortic aneurysm and bronchial asthma. On her second admission two and a half years later, her condition was the same. Roentgen examination revealed a large, round shadow in the right side of the chest, which was interpreted as a sacculated aneurysm of the first portion of the aorta. The patient was again seen in May, 1925, with the same picture. On her fourth admission, in April, 1926, she was found to be markedly dyspneic and orthopneic. Because of the persistence of the shadow in the right side of the chest over so long a period it was suggested that it might be a dermoid cyst of the mediastinum. At her fifth and last admission, dyspnea was extreme, and there was marked cyanosis. Roentgen examination showed that the shadow had grown considerably. Pulmonary edema developed and the patient died.

*Autopsy.*—Autopsy was performed nine hours later by Dr. Rabin. The body was that of a middle-aged white woman. The face was intensely cyanosed. There were prominent veins over the upper part of the abdomen and lower part of the chest. The lower extremities were very edematous. Owing to the limitations placed on the autopsy in the permit, the viscera were removed en masse through an abdominal incision. Therefore, no adequate description of the thoracic viscera in situ can be made.

The right side of the diaphragm extended to the sixth intercostal space. The right side of the pleural cavity contained a large amount of amber-colored, clear fluid. There were a number of fine fibrous bands between the upper lobe and the wall of the chest; the middle and upper lobes were fused by adhesions. Arising from the mesial aspect of the right upper lobe on a broad base and projecting into the pleural cavity, there was a large, whitish, oval tumor covered with a smooth membrane (fig. 3). It measured 19 by 10 by 10 cm. and was firm in consistency, giving the sensation of deep fluctuation. The tumor lay between the lung and the anterior mediastinal structures. Its upper pole extended to the dome of the pleural cavity and the lower pole almost to the diaphragm. The superior vena cava was compressed by the tumor; the ostium of the azygos vein was obliterated and represented by a dimple in the superior vena cava. The entire lung was displaced laterally and posteriorly, the upper and middle lobes being completely atelectatic. The capsule of the tumor was smooth and glistening and was continuous laterally with the pleura of the right upper lobe. In this region, compressed pulmonary tissue was visible beneath the capsule which was reflected from the mesial portion of the lobe onto the tumor for a distance of 3 or 4 cm. On the mesial and anterior surface, a thin patch of anthracotic lung tissue, measuring 116 by 3 cm., was seen beneath the capsule. Its continuity with the upper lobe could not be traced. The capsule covering the tumor was reflected mesially over the mediastinum and was continuous with the mediastinal pleura. Therefore, the free surface of the tumor was covered by pleura. Posteriorly, the neoplasm

bulged into the substance of the right upper lobe, from which it was sharply demarcated and could be separated with ease. At the hilus of the lung, however, a small portion of the tumor had forced its way between the bronchial cartilages into the lumen of the bronchus of the upper lobe to form a smooth polypoid projection covered with bronchial mucous membrane. This measured 1.5 cm. in length, 1 cm. in width, and 6 mm. in height. It pointed upward toward the bifurcation, totally occluding the lumen of the bronchus of the upper lobe and slightly narrowing the lumen of the bronchus of the lower lobe. The bronchi distal to the tumor contained mucopurulent material, but were not dilated. On section, the tumor was solid throughout and had a pinkish-gray, fleshy appearance,

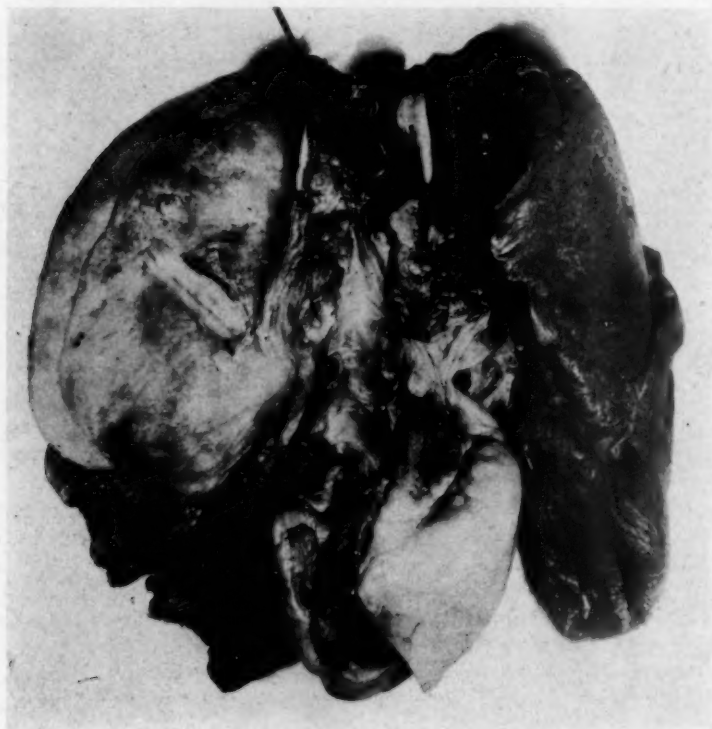


Fig. 3 (case 3).—Anterior view of the thoracic viscera, showing large tumor on mesial surface of right upper lobe with an area of flattened anthracotic lung tissue on the anterior surface. Note the hypertrophy of the right ventricle.

with many firm, ill defined nodules of firmer consistency. There were a few small, yellow, dry areas of necrosis. The bronchial lymph nodes showed a few areas of calcification. The left lung was large and well aerated.

The apex of the heart was formed mainly by the right ventricle, which was markedly hypertrophic and dilated. The pulmonary artery and its branches showed a considerable degree of atherosclerosis. The aorta showed numerous atherosclerotic patches.

The abdomen contained no free fluid. The abdominal viscera were markedly congested.

*Microscopic Examination of Tumor.*—Under low power magnification (fig. 4), the tumor appeared to consist of an edematous tissue, rich in fibers, beset with numerous veins and capillaries and very rich in cellular elements. The cells were in part uniformly distributed; in places, they were gathered together in small nests (fig. 4A). There was a dense network of parallel and intersecting wavy fibers, which were occasionally collected in loose bundles, especially about the blood vessels, which were surrounded by a mantle of longitudinal fibers. The fibers stained red with van Gieson's stain, blue with Mallory's aniline-blue-fuchsin, and reddish brown with phosphotungstic acid hematoxylin. Prominent among the cells were spindle-shaped elements with long drawn out cytoplasm and elongated oval nuclei with infolded nuclear membranes and a scanty fine chromatin network containing small nucleoli. These could easily be identified as fibroblasts. They were uniformly distributed over the entire section and lay in close relationship to the collagen fibers, to which they were often closely attached. Often the fibers seemed to be continuous with the finely drawn out cytoplasm. These cells were often very large, with several protoplasmic processes and bizarre, remarkably large nuclei, and occasionally there were multinucleated giant cells.

Between the fibers there were often found cells, either singly or in loosely connected groups, of a round or oval shape averaging from 8 by 8 to 8 by 16 microns, with abundant basophil, vacuolated cell bodies (Fig. 4C). These were often acidophil about the eccentrically situated nuclei. The nuclei were small and round, measuring 2.5 microns in diameter. They contained distinct, coarsely granular chromatin, which occasionally was gathered about an indistinct nuclear membrane. Occasionally the cells showed pseudopodia-like processes. Often they contained two nuclei.

Furthermore, there were small cells with very dark, round nuclei and narrow cytoplasm, which could be identified as lymphocytes, in addition to a moderate number of eosinophil leukocytes, myelocytes and scattered nucleated red blood corpuscles, singly and in groups. Numerous capillaries in longitudinal and cross-section, and only a few larger veins completed the picture. Attached to the walls of the blood vessels there were occasional spindle-shaped cells with large spindle-shaped nuclei and scanty cytoplasm, having the appearance of fibroblasts, differing from them, however, by their somewhat darker nuclei and indistinct cell bodies.

Doubt as to the nature of the various histologic elements of this tumor can arise only as to the large round cells with abundant cytoplasm. A discussion of these cells is of importance because of their relation to the genesis of this neoplasm.

Although these cells resembled the mononuclear wandering cells of inflamed tissues (polyblasts of Maximow), they can scarcely be considered as such for a number of reasons: Sections of all parts of the tumor contained these cells in great numbers. In general, they were not found to lie in particular proximity to the blood vessels. The latter were not congested nor did they contain many leukocytes. There were no collections of emigrated blood cells in the tissues about the blood vessels. Moreover, in their morphology, the cells coincided exactly with the histiocytic wandering cells of embryonic connective tissue. This is shown by a comparison of their characteristics with the description

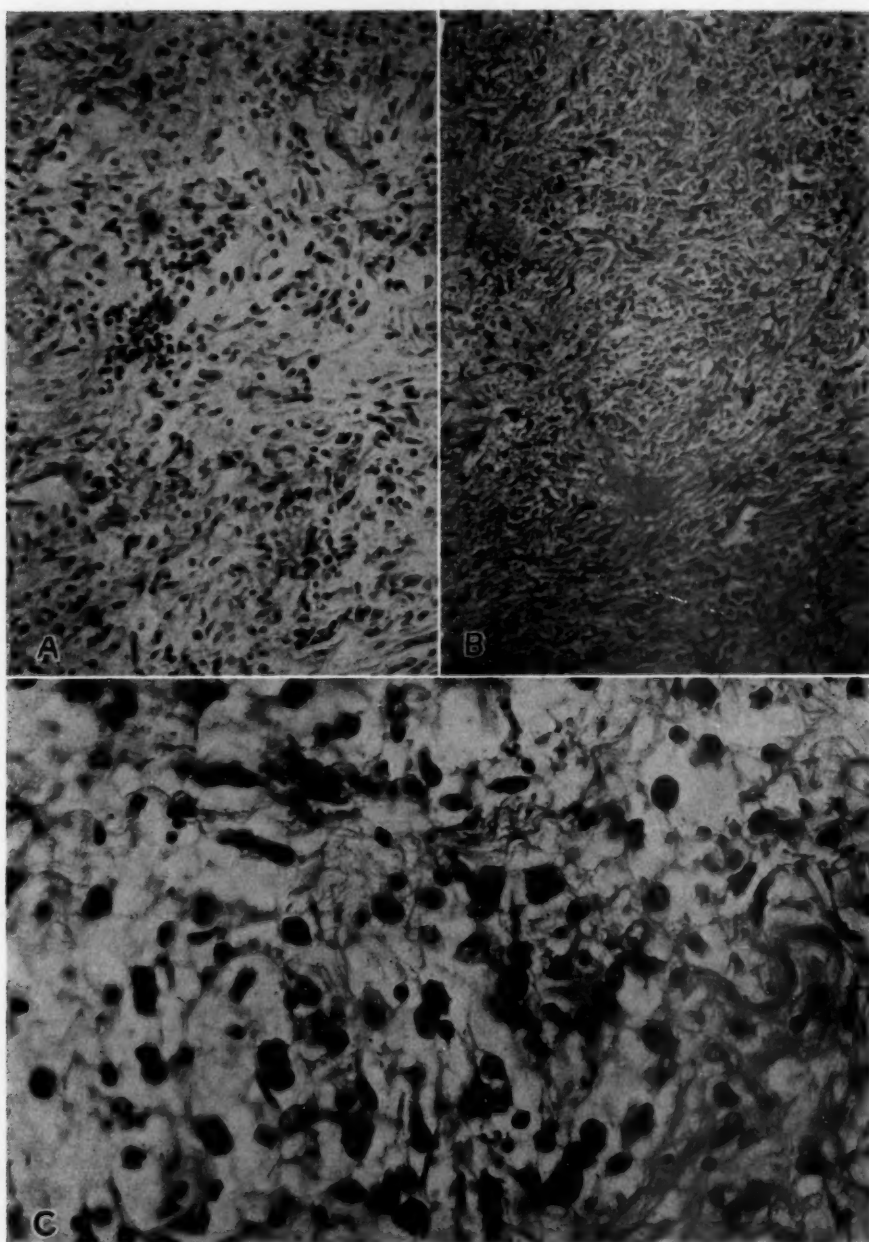


Fig. 4 (case 3).—*A* and *B*, low power views showing loose connective tissue containing a variety of cells; *C*, high power view showing fibroblasts, lymphocytes, connective tissue fibers and mononuclear cells, resembling histiocytic wandering cells. Note the resemblance to embryonal connective tissue.

of the latter by Maximow<sup>29</sup> (Das Aussehen des lockeren Gewebes bei Embryonen in der mittleren Periode der Schwangerschaft erinnert sehr an entzündetes mit Polyblasten infiltriertes Gewebe des Erwachsenen). (The appearance of the loose tissues in embryos during the middle period of pregnancy reminds one of inflamed tissues, infiltrated with polyblasts, in adults.)

The spindle cells described as resembling fibroblasts, lying in the vicinity of the blood vessels, resembled, in their localization and morphology, the undifferentiated perivascular mesenchymal cells of Maximow.

The cellular elements of the tumor in their morphology and in their arrangement throughout the stroma bore the closest resemblance to the loose connective tissue in the latter phases of embryonic life.

It is therefore justifiable to conclude that the tumor represents a neoplastic overgrowth of embryonic connective tissue. In this respect, it differs from the ripe fibroma, which structurally simulates mature connective tissue. However, it differs from the fibroblastic sarcoma in that it retains the typical structure of the mother tissue in contradistinction to the atypism of malignant connective tissue tumors.

**CASE 4.—History.**—R. M., a white man, 41 years of age, was admitted to Mount Sinai Hospital on Sept. 6, 1919, complaining of pain in the right side of the chest. The physician had aspirated the right side of the chest and withdrawn some bloody fluid. On admission to the hospital, the patient was dyspneic and on examination showed dilated venules over the right side of the lower part of the chest. There were signs of fluid in the right side of the chest. The edge of the liver was felt three fingers below the costal margin. Roentgen examination showed a large shadow almost completely filling the right side of the chest, presenting the appearance of a neoplasm. The patient was readmitted in April, 1930, complaining of increasing dyspnea and orthopnea. Examination showed the same signs as before. The liver was, however, larger, extending 15 cm. below the costal margin. The patient was intensely cyanosed. The lower extremities were very edematous. There were varicose veins over both thighs. The patient died, two days after admission to the hospital, of cardiac failure.

**Autopsy.**—Autopsy was performed nine hours later by Dr. Otani. The body was that of a middle aged man, slightly obese, in complete rigor mortis. There was marked cyanosis of the head and neck, with slight clubbing of the fingers and toes. There was no edema. The thoracic organs had to be removed through an abdominal incision, and no direct inspection of the thoracic viscera in situ was possible. The right side of the diaphragm extended to the sixth, the left to the fifth, interspace. The right side of the chest was filled by a soft tumor mass exceeding the size of a man's head, which was adherent to the parietal pleura of the anterior and lateral walls of the chest. There was a thick band between the lower surface and the diaphragm, and a flat band binding the upper pole of the tumor to the inferior border of the middle lobe. The mass measured 25 by 19 by 12 cm. and was shaped like a cast of almost the entire right pleural cavity

29. Maximow, A., in Moellendorff, W.: *Handbuch der mikroskopischen Anatomies des Menschen*, Berlin, Julius Springer, 1927, vol. 2, pt. 1, p. 504.

with the exception of the dome, which was occupied by the compressed upper lobe. It was encapsulated by a smooth, fibrous membrane that was continuous with the visceral pleura of the right lower lobe (fig. 5). It was connected with the anterior portion of the inferior border of the lower lobe by a flat pedicle of lung tissue, 6 cm. in breadth, 5 cm. in length and 6 mm. in thickness. The lung tissue of this pedicle continued for a distance of about 10 cm. as a gradually thinning shell over the posterior surface of the tumor beneath the pleural capsule. The tumor developed in front of the lower lobe. Its base rested on the diaphragm. Its upper pole displaced the upper and middle lobes into the dome of the pleura. It grew between the lobes in the large fissure, the upper and the middle lobe resting on the front of the cranial portion of the tumor. Arising in a similar manner from the base of the lower lobe was a tongue-shaped second tumor



Fig. 5 (case 4).—Posterior view of right lung, showing large and small lipomas arising from the subpleural areolar tissue and attached to the lower lobe by pedicles of lung tissue.

measuring 7.5 by 4 by 2.5 cm. This also was covered by pleura reflected from the lower lobe, and showed beneath the pleural capsule a continuation of pulmonary parenchyma for a short distance from its point of origin. On section, both tumors were composed entirely of grapelike nodules of yellow fat tissue (fig. 6). It was richly vascularized by wide sinuses filled with coagulated and liquid blood, which were continuous with the pulmonary blood vessels.

The left pleural cavity contained no fluid, and the lung was free from adhesions. It was slightly compressed from the displacement of the mediastinal structures to the left side by the tumor occupying the right pleural cavity.

The upper portion of the parietal pericardium on the right side was adherent to the tumor. The pericardial sac was empty. The heart weighed 480 Gm. The

apex was formed by the right chamber. The right ventricle showed an extreme degree of hypertrophy and dilatation. The right auricle was markedly dilated; the tricuspid ring was very wide. The pulmonary artery measured 7.5 cm. at its point of origin and showed slight atherosclerosis. The left ventricle was slightly hypertrophic. The valves of the heart were free from changes.

The abdominal viscera showed marked congestion.

*Microscopic Examination of Tumor.*—Microscopic examination of the tumor showed the typical structure of a lipoma.

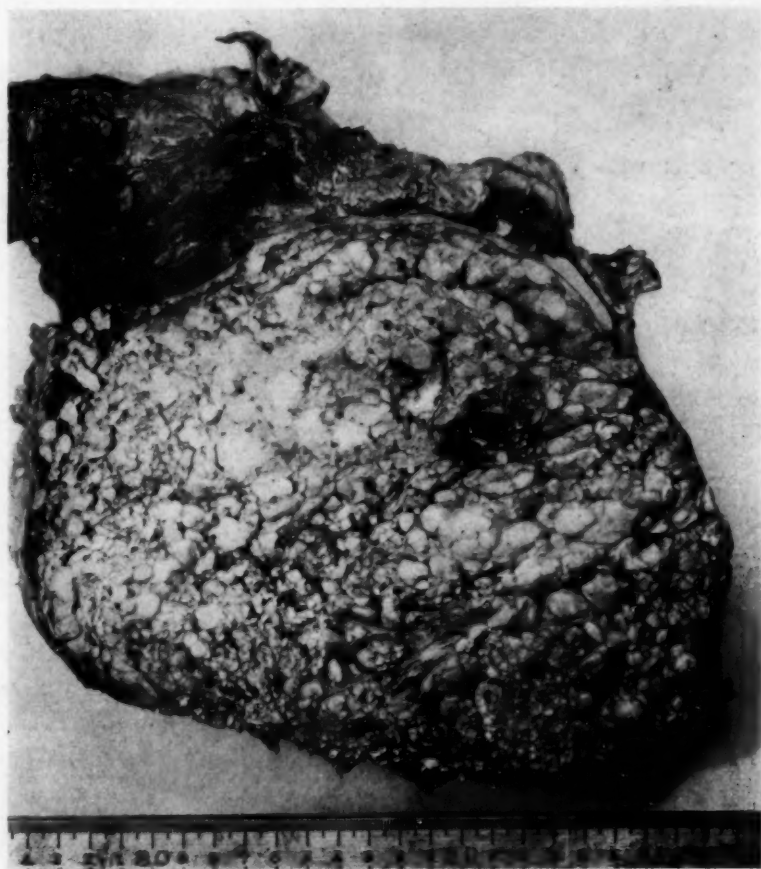


Fig. 6.—Same tumor as in figure 5 on cross-section, showing typical appearance of lipoma.

#### COMMENT ON CASES 1 TO 4

In their slow progress and their gross anatomical features, because of which they are designated as giant tumors of the pleura, these cases conformed with the cases in the literature. In three of the cases, the localization of the tumor, as a pedunculated mass projecting into the pleural cavity and covered everywhere by the visceral pleura, showed

conclusively the point of origin of the neoplasm to be the subserous pleural tissue. At the point of attachment of the tumor, the lung was drawn out in a pedicle that spread out over the tumor for a short distance, but was separated everywhere by the tumor capsule. In the two fatal cases, death was due to the mechanical interference with the pulmonary circulation caused by the enormous tumor, resulting in failure of the right ventricle.

The microscopic examination of these growths, in accordance with the other observations in the literature, showed them to be of mesenchymal origin. There were, however, differences in the type of tissue of which they were formed. The first three were connective tissue tumors. The first was a fibroblastic neoplasm of great cellularity. The tumor cells were uniform in type and showed no mitotic figures. The occasional infiltration of the capsule, however, indicated that the tumor possessed malignant properties, and fibrosarcoma of a low grade of malignancy was diagnosed. It is significant that the second, at its first examination, showed a similar picture. Specimens of the tumor removed four years after the partial resection of the neoplasm showed remarkable changes in the histology, indicating a highly malignant character, which was also evidenced by the formation of metastases in the other lung. It is possible that the repeated surgical interference in removing portions of the tumor was responsible for the malignant transformation of the tumor. This has been observed commonly after incomplete removal of certain fibroblastic tumors. Intensive radiotherapy did not arrest the further growth and dissemination of the neoplasm.

The third tumor, however, in spite of its embryonal histologic structure, was benign. As has been stated, the microscopic appearance of the tumor conformed fully with that of embryonal connective tissue in the later stages of its development. It did not show any qualitative aberration from this tissue, and the quantitative proportions of the cellular elements and fibrillar structures were identical with those of normal embryonal connective tissue of this phase. The long clinical course of at least twenty years' duration and the absence of any infiltration of the surrounding tissue confirmed the benign nature of the growth.

The fourth tumor was a simple lipoma, which caused death merely because of the tremendous proportions to which it had grown. Although there are no reports of giant fatty tumors of the visceral pleura in the literature, the origin of such a tumor from the subserous areolar tissue of the visceral pleura is not surprising. The development of fat tissue in the edges of the lung in obese patients is not uncommon. Its significance in relation to the histogenic potentialities of the undifferentiated

perivascular mesenchyme in this region has been commented on by Wassermann<sup>30</sup> in his elaborate study on the development of fat tissue.

#### DIFFUSE PLEURAL NEOPLASMS

Since the first description by Wagner<sup>31</sup> in 1870, there has arisen a controversy concerning the oncology of primary diffuse pleural neoplasms, which has grown with succeeding case reports and has lasted to the present day. The lack of agreement regarding the classification of these tumors has been caused by the wide variations in the appearance of the growths both grossly and microscopically. Some appear as epithelial growths, others as of connective tissue origin, and others seem to belong to neither class or to both. Whether the point of origin lay in the superficial lining cells of the pleura (mesothelium), in the subserous connective tissue or in the lymphatic endothelium has been a source of dispute. This, together with the polymorphic picture, has given rise to confusion, illustrated by the varied nomenclature which has been applied to these tumors. Krumbein<sup>32</sup> collected thirty different names for the tumors under discussion in his exhaustive study of the reported cases. The names applied most frequently, endothelioma, endothelial carcinoma, carcinoma, sarcoma, lymphangitis proliferans, sarcocarcinoma and mesothelioma, are indicative of the different morphologic pictures and of the different opinions of authors as to the point of origin. To make this confusion more complete, there have been included in the literature on primary tumors of the pleura a number of cases that, on critical examination, are proved to originate definitely in the lungs or in the bronchi.

This situation was clarified to a considerable degree by the critical review of all the cases in the literature by Robertson<sup>33</sup> in 1923. From an independent review of the literature we conclude, as did Robertson, that a considerable proportion of the cases reported were really cases of metastatic tumors of the pleura, and that all tumors of the pleura should be considered as metastatic if there is present in one of the viscera a neoplasm that can be considered a primary neoplasm. The belief in the nonexistence of "endothelioma" arising from the subserous lym-

30. Wassermann, F.: Die Fettorgane des Menschen, *Ztschr. f. Zellforsch u. mikr. Anat.* **3**:235, 1926.

31. Wagner, E.: Das tuberkelähnliche Lymphadenom, *Arch. f. Heilk.* **11**:497, 1870.

32. Krumbein, C.: Ueber die Natur der Deckzellen der serösen Häute—Untersucht an Hand eines primären Pleuracarcinoms, *Virchows Arch. f. path. Anat.* **249**:400, 1924.

33. Robertson, H. E.: Endothelioma of the Pleura, *J. Cancer Research* **8**:317, 1923-1924.

phatics is also concurred in. However, we disagree with the extreme point of view that no tumor of an epithelial structure can originate primarily in the pleura, and that the serosal lining cells cannot be the source of such tumors.

A case which has come under our observation showed structural peculiarities that are of interest in this connection.

#### REPORT OF CASE

*History.*—R. Z., a woman, 26 years old, was admitted to Mount Sinai Hospital on Aug. 22, 1929, complaining of pain in the left side of the chest from which

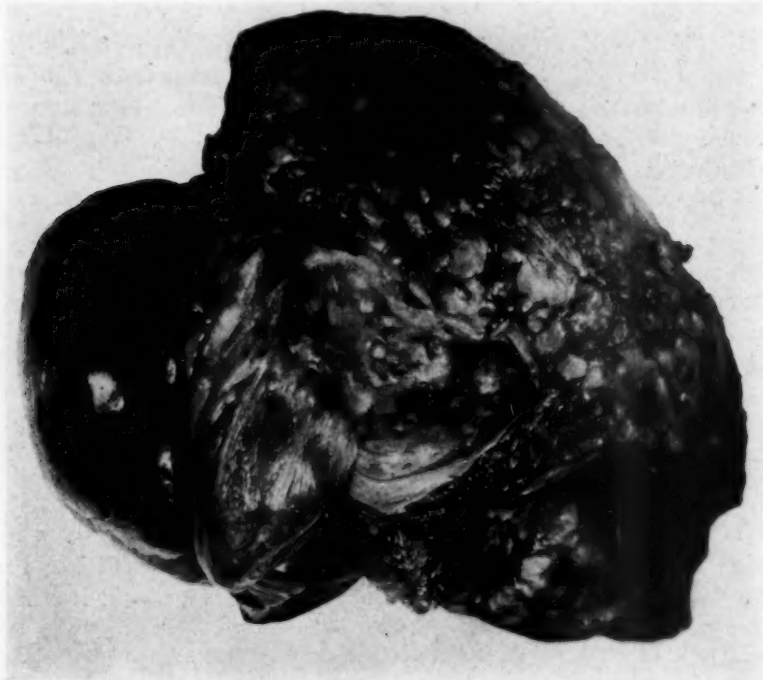


Fig. 7 (case 5).—Anterior view of the thoracic viscera, showing diffuse growth of a mesothelioma of the left pleura. The heart has been reflected to the right in order to show the infiltration of the pericardium.

she had suffered for a period of eleven months. Because of this ailment, she had been admitted to another hospital, where a rib resection was performed and radiotherapy advised. She subsequently received seven treatments at another hospital. On admission, she was weak and dyspneic. She had a temperature of 102 F. The left side of the chest was very prominent, the intercostal spaces obliterated. There was flatness to percussion over the entire left side of the chest, with the exception of the left apex, anteriorly, where the percussion note was tympanitic. Breath sounds were absent. The heart was displaced to the right side; the right border was situated 3 inches (7.5 cm.) to the right of the midline. The spleen was

palpable about 2 cm. beneath the left costal margin. Roentgen examination of the chest showed a diffuse shadow over the entire left pulmonary field, with a marked displacement of the heart to the right side. An exploratory puncture was performed. The needle met with great resistance. No fluid was obtained, but a small piece of tissue was withdrawn with the aspirating needle. The diagnosis made at this time was that of a neoplasm of the pleura.

Microscopic examination of the fragment of tissue showed it to be composed of irregular spindle cells with intercellular fibrous stroma. The cells varied in size, shape and staining capacity. Most of the nuclei were spindle-shaped. However, some were more rounded and irregular. In general, the nuclei contained

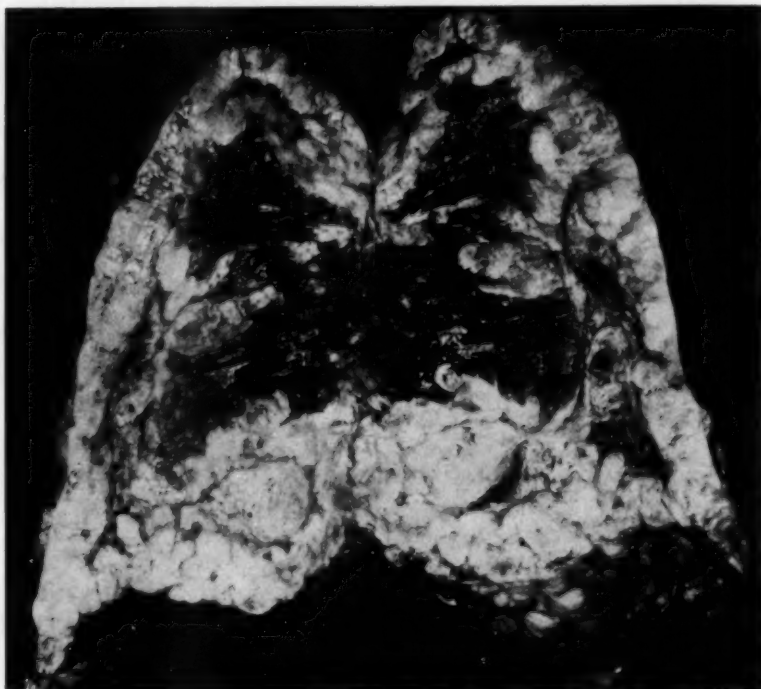


Fig. 8 (case 5).—Coronal section showing the complete encasement and infiltration of the lung by tumor.

finely divided chromatin with a distinct nuclear membrane. The diagnosis from this histologic specimen was fibrosarcoma.

The course was rapidly downhill. The patient became weaker, her fever persisted, and she became increasingly anemic. She was given an injection of Coley's vaccine. Three days later her temperature rose very sharply to 109 F., and she died.

*Autopsy.*—Necropsy was performed on Sept. 10, 1929, by Dr. S. Otani. The body was that of a well developed and fairly well nourished white woman. The left side of the chest bulged forward markedly and was resistant to pressure. The mucous membranes were pale. There was slight cyanosis of the face. The fingers and toes showed no clubbing. There was a scar of an old rib resection

in the posterior portion of the left side of the chest. There was a small, but deep, decubitus ulcer over the sacrum, with bone exposed. The diaphragm rested at the fifth rib on the right side and at the sixth rib on the left side.

Owing to a limitation of the permission for necropsy, the organs were removed through an abdominal incision; therefore, no exact observations could be made of the intrathoracic situs. There were about 40 cc. of clear fluid in the right side of the chest and a few fibrous adhesions over the middle and upper lobes. The right lung showed some collapse of the lower lobe. There was a small, whitish nodule in the pleura of the middle lobe. The left side of the pleural cavity was entirely obliterated, but it was possible to separate the lung from the wall of the chest. The parietal pleura was fused with the visceral layer, except at the base. It was composed of nodular tumor tissue which infiltrated the diaphragm and the wall of the chest between the ribs, especially in the region of the operative scar. The left lung was completely ensheathed by firm, nodular, whitish, fibrous tumor tissue, which measured from 4 to 15 cm. in thickness, the entire mass weighing about 4 Kg. (fig. 7). It measured 30 cm. in the longitudinal, 17 cm. in the frontal, and 15 cm. in the sagittal, diameters. The tumor infiltrated the periphery of the lung extensively in an irregular manner, in places extending into the center of the lung. On various coronal sections, the lung parenchyma appeared compressed and extremely irregular in outline, because of the extensive invasion by neoplasm (fig. 8). The bronchi showed neither infiltration nor narrowing of the lumen. The lymph nodes at the hilus of the lung were slightly enlarged and anthracotic; on section, some showed infiltration by white tumor tissue.

The posterior portion of the parietal pericardium was encased and infiltrated by tumor nodules. The pericardial cavity measured 13.5 cm. in its long axis and 10 cm. at its widest portion. The heart was small and atrophic and displaced to the right. The epicardium was covered with a fine fibrinous exudate. The columnae carneae of the left ventricle were markedly flattened and the papillary muscles atrophic. The arch and thoracic portion of the aorta were firmly fixed by the tumor and slightly narrowed.

The peritoneal surface of the left portion of the diaphragm showed nodular infiltration by the neoplasm, which involved the retroperitoneal tissues in this region and surrounded the left suprarenal capsule and the upper portion of the left kidney. There was no fluid in the peritoneal cavity.

The weight of the liver was 2,570 Gm. It showed marked congestion, but no metastases.

The weight of the spleen was 300 Gm. It was about twice the normal size and firm in consistency. The capsule showed a number of scattered white plaques. The pulp was congested.

Each kidney weighed 200 Gm. The capsule of the left kidney showed infiltration by the tumor. The capsule on both sides stripped easily, revealing smooth surfaces. There was no infiltration of the kidneys by tumor tissue.

The left suprarenal gland was surrounded by tumor tissue, but not infiltrated. The right showed no abnormality.

The uterus showed a small, white, fibrous nodule on the fundus. The endometrium was smooth and pale. The ovaries and tubes appeared normal.

The structure of the pancreas was natural, the consistency firm. No evidence of tumor was seen.

The gastro-intestinal tract was normal.

*Microscopic Examination of Tumor.*—Sections were taken from various portions of the tumor, including the infiltrated lung. Sections were also taken of the lining of the pleural cavity in order that a search might be made for the pleural mesothelium. The latter was absent. The section showed only tumor tissue, the surface of which was necrotic and covered by fibrin.

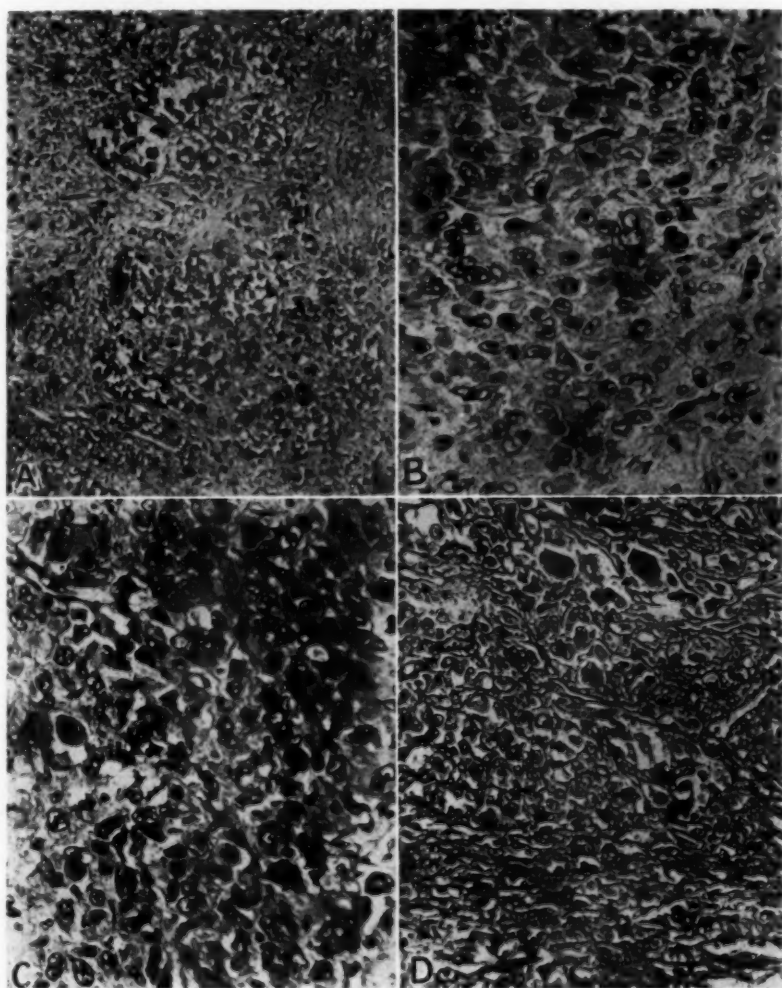


Fig. 9 (case 5).—Microscopic sections illustrating the epithelial nature of portions of the tumor: *A*, cells arranged in nests; *B*, epithelial characteristics, polygonal cells with abundant cytoplasm and vesicular nuclei with large nucleoli, arranged in rows; *C*, same cell characteristics as in *B*, and, in addition, coarse mitotic figures; *D*, Mallory's stain showing intercellular fibers between epithelial-like cells and multinucleated tumor giant cells.

The material was fixed in Zenker-Helly's solution and formaldehyde, and was embedded in paraffin. The sections were stained with hematoxylin-eosin, and by van Gieson's, Mallory's aniline blue-fuchsin, the phosphotungstic-hematoxylin and the Bielschowsky-Maresch silver impregnation methods.

Various portions of the tumor showed different characteristics. In general, the tumor was composed of irregular cells with large nuclei (fig. 9*B* and *C*). The

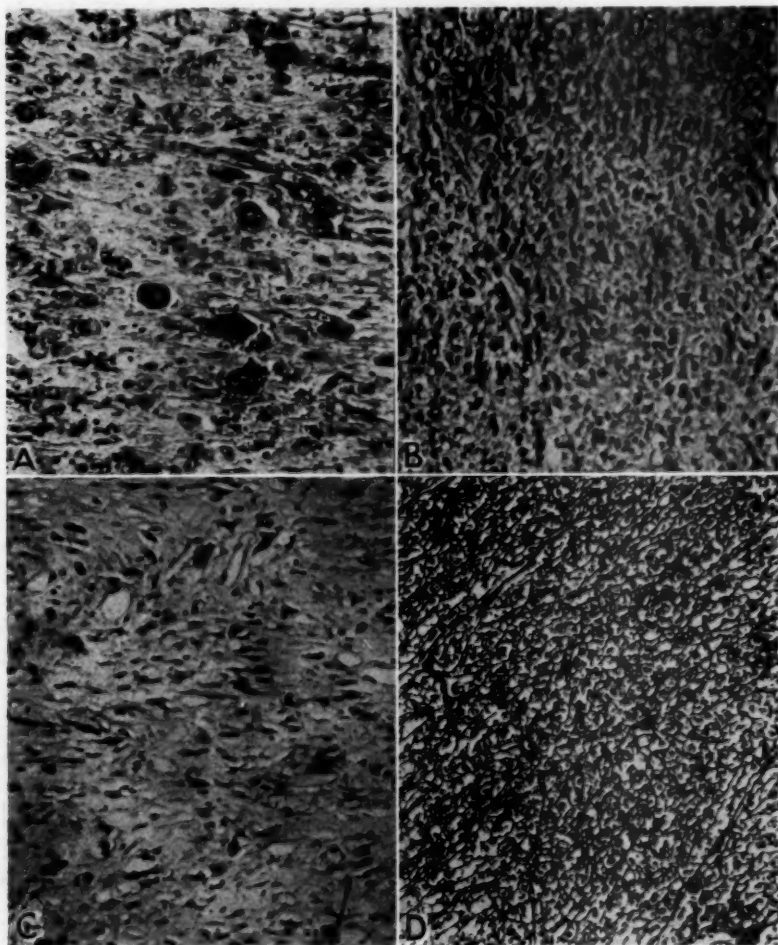


Fig. 10 (case 5).—Microscopic sections illustrating sarcomatous portions of tumor: *A*, polymorphous appearance of elements with large atypical giant cells and abundant stroma; *B*, fibroblastic appearance of tumor cells in a cellular area; *C*, flattened cells of fibroblastic appearance with dense stroma; *D*, Bielschowsky stain showing fibers surrounding each cell.

cells varied considerably in size, from 11 by 7 to 21 by 12 microns, with nuclei varying from 7 by 7 to 15 by 10 microns. In places, the cells were flattened and in other places rounded. The nuclei also varied in size and shape. They pos-

sessed a sharp nuclear membrane, which was often infolded. The nuclei were pale. The chromatin network was scanty. The nuclei contained one or more distinct nucleoli (fig. 9B). Some of the nucleoli were exceedingly large. Many of the cells contained two or more nuclei of the same appearance. There were many coarse mitotic figures (fig. 9C). The cytoplasmic outline was very hazy. There were fine cytoplasmic processes, which, in the specimen stained with hematoxylin-eosin, seemed to blend with intercellular fibers.

The cells also varied in their arrangement. In some sections there were areas in which the cells were closely approximated with scant intercellular material. This, together with the characteristics of the nuclear structure, gave the appearance of an epithelial new growth. In places, the cells lay in nests, forming an alveolar arrangement (fig. 9A). In other places, they were arrayed in rows, a trabecular arrangement. Here also the arrangement of the cells and the nuclear structure gave the appearance of an epithelial growth (fig. 9B).

In sections stained by the Mallory aniline-blue method or impregnated with silver according to Bielschowsky-Maresch, a network of fibers surrounding almost every cell was demonstrated (fig. 9D). In order to trace the origin of the fibers, the nests of tumor cells within the adjacent lung tissue were examined. Here not every cell was surrounded by fibers. However, the cytoplasm of some of the cells showed a bluish violet tint (with Mallory's aniline-blue stain), and occasionally one could recognize bluish specks within the cytoplasm with a condensation of bluish material at the edges of the cells. Such an appearance was not found in the cells that were surrounded by fully developed fibers.

In places, the cells assumed a bizarre form (fig. 10A). They were very irregular, and there were many multinucleated giant cells, with considerable fibrillar tissue between the cellular elements. There were, in addition, a number of thin-walled capillaries and occasional flattened fibroblasts.

In other places, the cells were markedly flattened and elongated (fig. 10B and C). The nuclei also were flattened and elongated, and the chromatin network was compressed and appeared more compact, giving the nuclei a darker appearance. The infolding of the nuclear membrane was more prominent in these regions. In these portions the fibers, which were more scanty and formed only an incomplete network in the other portions of the specimen, were numerous. Wavy fibers, 1 micron in thickness and running longitudinally, were seen between the cells.

In the section impregnated with silver, the fibers were seen everywhere between the cells (fig. 10D). In places, the fibers were condensed to form thick bands. Here the cells were compressed and fewer in number.

#### COMMENT ON CASE

This case belongs to the group of diffuse pleural neoplasms which completely ensheath the lung. Its primary origin in the pleura is beyond question. Although the autopsy was limited to the abdomen and thoracic viscera, there was no clinical suspicion throughout the entire course of the illness of any new growth in any other region of the body. In the organs that were examined there was no other growth that could possibly have been considered as primary. Moreover, the histologic picture conformed fully with that of some of the undoubted primary pleural tumors described in the literature.

The striking peculiarity of the histologic picture was the fact that it was composed of cells of an epithelial appearance, which, however, were almost everywhere separated from each other by collagen fibers. In places these cells were arranged in alveolar nests or in rows, with only a scanty incomplete fibrillar network. In other places, however, the cells were remarkably flattened, with a marked development of intercellular tissue, giving the appearance of fibroblastic tissue. The intercellular fibers appeared to be formed by the tumor cells themselves. This was indicated by the absence of other fiber-forming cells and by the observation of fibril development within the cytoplasm of the cells situated in the peripheral portions of the tumor.

The predominant cell type was a large polygonal cell, often with abundant cytoplasm. The nucleus was large. The chromatin was sparse and finely divided, giving the nucleus a pale vesicular appearance. The chromatin was condensed at the periphery of the nucleus, forming a very distinct nuclear membrane which was irregular and infolded. There were many large nucleoli. In spite of the presence of the intercellular fibers these cells generally differed from fibroblasts. The appearance was more that of epithelial cells, and it corresponded to the description of the serosal lining cells as given by Maximow.<sup>29</sup>

Among the primary pleural neoplasms described in the literature there are a number the descriptions of which are similar to that of the one reported here. Cases of such tumors have been reported by a number of observers. Bernard<sup>34</sup> and Gutmann<sup>35</sup> gave excellent descriptions of the epithelial-like nucleus and of the reticulum which surrounded each cell. They appreciated the peculiar nature of the tumors, and each considered his case unique in the literature. Kornitzer<sup>36</sup> regarded his case as that of simple endothelioma in spite of the fact that his description is identical with that given here. Podack<sup>25</sup> and Boehme<sup>37</sup> remarked that their tumors contained islands of epithelial cells, but also showed sarcomatous qualities. They concluded, however, that they were dealing with a proliferation of lymphatic endothelium, which is closely related to the mesenchyme. The case reported by MacMahon and Mallory<sup>38</sup> as a pleural sarcoma is found, on examination of their plates, to simulate

34. Bernard, cited by Robertson (footnote 33).

35. Gutmann, C.: Beitrag zur Kenntnis der primären malignen Tumoren der Pleura, *Deutsches Arch. f. klin. Med.* **75**:337, 1902-1903.

36. Kornitzer, E.: Zur Kenntnis der Pleuratumoren, *Berl. klin. Wchnschr.* **56**:1039, 1919.

37. Boehme, M.: Primäres Sarcocarcinom der Pleura, *Virchows Arch. f. path. Anat.* **81**:181, 1880.

38. MacMahon, H. E., and Mallory, G. K.: Fibrosarcoma of the Pleura, *Am. J. Path.* **4**:387, 1928.

our case very closely. Glockner's<sup>39</sup> two cases of endothelioma of the peritoneum prove to be of a similar nature.

That the pleural lining cells are capable of producing tumors with both epithelial and connective tissue characteristics was pointed out by Paltauf,<sup>40</sup> Borst<sup>41</sup> and Kaufmann.<sup>42</sup> Miller and Wynn,<sup>43</sup> in reporting a case of tumor of the peritoneum, were the first to advance the opinion that a neoplasm of the lining cells was able to present both epithelial and fibroblastic characteristics, because of the embryologic relationship of these cells to the mesoderm. This opinion was also held by Zeckwer<sup>44</sup> in her report of a case of pleural mesothelioma. A consideration of the embryonal development and of the recent investigations of the potentialities of the mesothelial cells corroborates this view.

According to the accepted embryologic studies of Hertwig, the lining of the pleuropericardial cavity develops from the celomic epithelium, which is developed by the splitting of the mesoderm (not the mesenchyme as is stated by Kaufmann, who is quoted by Robertson<sup>33</sup>). There is no basement membrane between this celomic epithelium and the underlying mesenchyme, which later also arises from the mesoderm and which gives rise to connective tissue, the blood and the endothelium of the lymphatic and blood vessels. The close genetic relationship between the celomic epithelium and the underlying mesenchymal tissue is therefore apparent.

Since this epithelial tissue has its ultimate origin in the mesoderm, and since, as later research has shown, it has potentialities which differentiate it from the ectodermal or endodermal epithelium, it has been called mesothelium. It should be noted that in its development it has no direct relation to the endothelium of the lymph spaces, which is a highly specialized form of mesenchyme.

Early observers believed that they could show transitions from the mesothelial coverings of the pericardium to fibrous tissue. The pictures, however, were not convincing.

Since the work of Marchand<sup>45</sup> in the production of inflammatory reactions in the peritoneum by the introduction of spores of *Lycopodium*,

39. Glockner, A.: Ueber den sogenannten Endothelkrebs der serösen Häute (Wagner-Schulz), Ztschr. f. Heilk. **18**:209, 1897.

40. Paltauf, R.: Ueber Geschwülste der glandula carotica, Beitr. z. path. Anat. u. z. allg. Path. **11**:277, 1892.

41. Borst, M.: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902, vol. 1, p. 287.

42. Kaufmann (footnote 4, p. 386).

43. Miller, J., and Wynn, W. H.: A Malignant Tumor Arising from the Endothelium of the Peritoneum and Producing a Mucoid Ascitic Fluid, J. Path. & Bact. **12**:267, 1908.

44. Zeckwer, I. T.: Mesothelioma of the Pleura, Arch. Int. Med. **34**:191, 1924.

45. Marchand, F.: Die Veränderungen der peritonealen Deckzellen nach Einführung kleiner Fremdkörper, Beitr. z. path. Anat. u. z. allg. Path. **69**:1, 1921.

a controversy has arisen as to the potentiality of the mesothelium for displaying mesenchymal characteristics and for forming intercellular fibers. Marchand<sup>46</sup> in his early work, which was checked by more careful later observations, believed he was able to demonstrate this beyond a doubt.

Recently, Cunningham,<sup>47</sup> who has been the chief exponent of the specificity of the mesothelial cells as epithelium, has cast doubt on the conclusions drawn from these studies based on the irritation of the serous membranes by foreign bodies. He was able to show remarkable pictures of hyperplasia of the mesothelial cells by the injection of irritants into the serous cavities. Other authors have called attention to the fact that the mesothelium of lower animals may become so differentiated as epithelial structures that they bear cilia. Stratified epithelial-like proliferations have been noted over the peritoneal surface of the diaphragm and in the beadlike thickenings on the splenic capsule. Cunningham felt that the connective tissue growth that followed irritation of the pleura and peritoneum was due to the degeneration of the serous lining cells and to proliferation of the subserous connective tissue. By using the silver impregnation method to demonstrate what he considered to be the outline of the mesothelial cells, he was able to demonstrate the rounding of these cells, their degeneration, the separation of the cells from each other and the formation of fibroblasts between them. He therefore considered that this fibroblastic proliferation originated from the connective tissue underneath the lining cells and not from the mesothelial cells.

Maximow,<sup>48</sup> in his latest work, pointed out the difficulty of drawing conclusions from such observations. By means of tissue cultures he was able to observe direct transitions from the mesothelial cells to fibroblasts. The degenerative changes noted by Cunningham were observed, but after a longer or shorter interval of time, the rounded mesothelial cells gradually developed processes, became of fibroblastic appearance and developed collagen fibers.

This constitutes final proof of the mesenchymal potentialities of the mesothelium. These potentialities, proved both by embryologic and by experimental evidence, explain the peculiarities presented by the

46. Marchand, F.: Ueber die Beziehungen der pathologischen Anatomie zur Entwicklungsgeschichte, besonders der Keimblattlehre, *Verhandl. d. deutsch. path. Gesellsch.* **2**:38, 1899.

47. Cunningham, R. S.: The Changes in the Omentum of the Rabbit During Mild Irritations with Especial Reference to the Specificity of the Mesothelium, *Bull. Johns Hopkins Hosp.* **33**:257, 1922; The Effects of Chronic Irritations on the Morphology of the Mesothelium, *ibid.* **35**:11, 1924.

48. Maximow, A.: Ueber das Mesothelium (Deckzellen der serösen Häute) und die Zellen der serösen Exudate, *Arch. f. exper. Zellforsch.* **4**:1, 1927.

tumor which has been reported here. That epithelial structures may develop from the mesothelium in accordance with the observations of Cunningham cannot be denied. The formation of primary epithelial tumors of the pleura as reported by Harris,<sup>49</sup> Benda<sup>50</sup> and Sprunt<sup>51</sup> is explainable on this basis. In fact, the illustrations accompanying the reports of the latter two present a close resemblance to the epithelial hyperplasia produced experimentally by Cunningham.

The occurrence of tumors that present both epithelial and mesenchymal characteristics, as in our case, and in those reported in the literature and referred to here, therefore, is not surprising. Even diffuse sarcomas, such as described by Cohen,<sup>52</sup> Deruschinsky,<sup>53</sup> Schwalbe,<sup>54</sup> Regnault,<sup>55</sup> Petriaux,<sup>56</sup> Oelrick<sup>57</sup> and Brandam,<sup>58</sup> including the chondrosarcomas of Busse,<sup>59</sup> Schultze<sup>60</sup> and Fallscher,<sup>61</sup> may conceivably be explained on the same basis of the developmental potentialities of the mesothelial cells. The similarity of these diffuse sarcomas in their gross appearance to the other diffuse pleural tumors makes it probable that they also originate from the surface and not from the subserous areolar tissue. It is to be expected that tumors arising from the surface would be diffusely spread throughout the pleural cavity. On the other hand, tumors arising subpleurally are apt to remain localized. It is significant that the localized neoplasms of the pleura described

49. Harris, T.: A Contribution to the Pathology and Clinical Features of Malignant Disease of the Pleura, *J. Path. & Bact.* **2**:174, 1893-1894.

50. Benda, C.: Ueber das primäre Carcinom der Pleura, *Deutsche med. Wchnschr.* **23**:324, 1897.

51. Sprunt, T. P.: Primary Carcinoma of the Pleura, *Bull. Johns Hopkins Hosp.* **22**:289, 1911.

52. Cohen, M.: Ein Fall von primären Fibrosarcoma der Pleura, *Inaug. Diss., Würzburg*, 1895.

53. Deruschinsky, S. F.: Primäres Sarkom der Pleura, *Deutsche med. Wchnschr.* **14**:52, 1888.

54. Schwalbe, E.: Zur Lehre von den primären Lungen und Pleurageschwülsten, *Deutsche med. Wchnschr.* **17**:1238, 1891.

55. Regnault, F.: Sarcome primitif de la plèvre, *Bull. Soc. anat. de Paris* **62**:528, 1887.

56. Petriaux, L.: Reflexions sur quelques cas de tumeurs de la plèvre, *Thèse de Paris*, 1893, p. 51.

57. Oelrick, I. D.: Ueber maligne Lungen- und Pleuratumoren, *Nord. med. Ark.*, 1903, vol. 3, nos. 3 and 8.

58. Brandam, J.: Contribución al estudio anatomo-clinico de los sarcomas primitivos de la pleura, *Rev. Soc. med. argent., Buenos Aires* **15**:237, 1907.

59. Busse, I.: Ueber ein Chondromyxosarcoma pleurae dextrae, *Virchows Arch. f. path. Anat.* **189**:1, 1907.

60. Schultze: Knorpel der Lungenpleura, *Inaug. Diss., Greifswald*, 1905.

61. Fallscher, Karl: Ueber einen Fall von Chondrosarkom der pleura, *Inaug. Diss., Bonn*, 1909.

in the first part of this article all arose subpleurally and were of undoubted connective tissue origin.

Most of the difficulty has been due to too much emphasis on the histologic picture and lack of appreciation of the point of origin. This conception of the unitarian origin of the diffuse neoplasms of the pleura eliminates the confusing experiences in classifying pleural tumors. It is therefore recommended that the term mesothelium, the term first applied by Adami, be accepted to designate all the diffuse neoplasms of the pleura that arise from the mesothelium, whether they appear to be composed of epithelium, connective tissue, or both.

#### SUMMARY

Primary neoplasms of the pleura are divided into localized and diffuse forms. The literature on giant tumors of the visceral pleura has been reviewed, and four new cases have been reported. These tumors are of mesenchymal structure and originate from the subpleural areolar tissue. Although, histologically, they usually present evidences of a low grade of malignancy, they progress very slowly and usually cause death by interference with the pulmonary circulation. They offer an opportunity for surgical removal.

Diffuse neoplasms of the pleura arise from the surface lining cells, the mesothelium, and should be designated mesothelioma. They may present the characteristics of epithelium, of connective tissue or of both. A case of the last type is reported. The complex structure of the tumor is explained by the varied potentialities of the mesothelial cells as shown by their histogenesis and by experiment.<sup>62</sup>

62. After the presentation of this paper, attention was drawn to the article of E. Kux (Zur Kenntnis der primären Geschwülste des Brustfells, *Virchows Arch. f. path. Anat.* **272**:650, 1929), who had previously emphasized the significance of the work of Maximow in explanation of three cases of pleural mesothelioma that showed both epithelial and fibroblastic characteristics.

## AVITAMINOSIS

### I. PATHOLOGIC CHANGES IN NURSING AND IN WEANED ALBINO RATS SUFFERING FROM VITAMIN B DEFICIENCY \*

BARNETT SURE, Ph.D.

FAYETTEVILLE, ARK.

HARVEY S. THATCHER, M.D.

LITTLE ROCK, ARK.

AND

DOROTHY J. WALKER, M.S.

FAYETTEVILLE, ARK.

During the last few years it has been definitely established <sup>1</sup> that the dietary factor which McCollum and Kennedy <sup>2</sup> in 1916 termed "water-soluble B" and which was later generally recognized as "vitamin B" is a complex composed of at least two distinct vitamins: one of these is relatively thermolabile and has antineuritic and growth-promoting properties; the other is more stable after heating under pressure, also possesses growth-promoting properties, and functions in the prevention and cure of pellagra-like symptoms in the rat. The former is also referred to as the antiberiberi, and the latter as the antipellagic, vitamin. The nomenclature of these dietary essentials has not yet been finally settled, but for the present we have adopted the terms recommended by the American Society of Biological Chemists,<sup>3</sup> i. e., the letter "B" to represent the antineuritic, and the letter "G" to indicate the antipellagic, factor.

Practically all of the literature on the pathologic changes resulting from vitamin B deficiency deals with the vitamin B complex,<sup>4</sup> and a

\* Submitted for publication, July 21, 1930.

\* Research paper 145, Journal Series, University of Arkansas.

\* From the Laboratory of Agricultural Chemistry, University of Arkansas, Fayetteville, and the Laboratory of Medical Pathology, University of Arkansas, Little Rock.

1. Smith and Hendrick: Pub. Health Rep. **41**:201, 1926. Goldberger; Wheeler; Lillie, and Rogers: Ibid. **41**:297, 1926. Goldberger and Lillie: Ibid. **41**:1025, 1926. Chick and Roscoe: Biochem. J. **21**:698, 1927. Sherman and Axtmayer: J. Biol. Chem. **75**:207, 1927. Hunt: Ibid. **78**:83, 1928. Evans and Burr: Ibid. **76**:263, 1928. Sure: Ibid. **80**:297, 1928. Salmon; Hays, and Guerrant: Etiology of Dermatitis of Experimental Pellagra of Rats, J. Infect. Dis. **43**:426, 1928. Sherman and Sandels: Proc. Soc. Exper. Biol. & Med. **26**:536, 1929.

2. McCollum and Kennedy: J. Biol. Chem. **24**:491, 1916.

3. Science **69**:276, 1929.

4. Jackson: The Effects of Inanition and Malnutrition on Growth and Structure, Arch. Path. **7**:1042, 1929; Ibid. **8**:81 and 273, 1929.

large part of it is concerned with work on pigeons;<sup>5</sup> hence, no attempt has been made to review any of this work. For a complete summary on the subject, the reader is referred to Jackson's recent review.<sup>4</sup> The only article dealing somewhat with the gross and microscopic changes resulting from uncomplicated vitamin B deficiency that has come to our attention since the completion of our study is that of Findlay,<sup>6</sup> but the greater part of his paper treats of the antipellagric factor, vitamin B<sub>2</sub>, which is the tentative nomenclature adopted by the English biochemists for this dietary essential.

The stimulus for our investigation of tissue changes in avitaminosis was the discovery by Sure and Schilling several years ago that the nursing young of the albino rat, the maternal diet of which contained an insufficient amount of the vitamin B complex for lactation, died without hemorrhages in the osteogenic tissues, particularly at the juncture of the occipital and parietal bones.<sup>7</sup> Therefore, the first study concerned itself with nursing young suffering from a deficiency of the vitamin B complex. In this connection, we examined only the histologic changes in the liver. Later, the perfection of a biologic method for the production of uncomplicated vitamin B deficiency in nurslings of the albino rat<sup>8</sup> enabled us to investigate the possible histologic effect of such avitaminosis. We then turned our attention to weaned and growing rats. In this communication, we summarize our observations on animals that have been deprived of the vitamin B complex and of vitamin B alone.

In previous publications, Sure, Kik and Walker, and Sure and Smith<sup>9</sup> demonstrated that in vitamin B deficiency and in deficiency of the vitamin B complex anhydremia develops, associated with a disturbance in hematopoietic function, although no definite anemia was established. This condition was encountered in nurslings, as well as in weaned animals. Sure and Smith<sup>10</sup> found an increase in the nonsugar reducing substances in uncomplicated vitamin B deficiency. The most marked biochemical change noted was a reduction in the glycogen content of the liver.<sup>11</sup>

The rations used and the results of the present investigation are summarized in tables 1 to 5 inclusive and in figure 1.

---

5. McCarrison: Indian Med. Res. Mem. No. 10, 1928, p. 1. Sundararajan: *Ibid.*, p. 59.

6. Findlay: *J. Path. & Bact.* **31**:353, 1928.

7. Sure and Schilling: Vitamin Requirements of Nursing Young: II. The Production of Beriberi in the Nursing Young (*Mus Norvegicus Albinus*) Associated with Hemorrhages, *Am. J. Dis. Child.* **35**:811, 1928.

8. Sure and Smith: *J. Nutrition* **1**:537, 1929.

9. Sure; Kik, and Walker: *J. Biol. Chem.* **82**:287, 1929. Sure and Smith: *Ibid.* **82**:307, 1929.

10. Sure and Smith: *J. Biol. Chem.* **84**:727, 1929.

11. Sure and Smith: *Proc. Soc. Exper. Biol. & Med.* **27**:861, 1929.

TABLE 1.—Composition of Rations

Components	Stock Diet 1*	Stock Diet 6*	Ration						
			1009†	1654	1145	1438	1432	1676	1646
Whole wheat.....	27.0	27.0							
Rollod oats.....	26.0	26.0							
Yellow corn.....	25.0	25.0							
Rice polishings.....		5.0							
Linseed oil meal.....	15.0	15.0							
Commercial casein.....	5.0	5.0							
Cod liver oil.....	1.0	1.0							
Sodium chloride.....	0.5	0.5							
Calcium carbonate.....	0.5	0.5							
Casein (purified)§.....			20	18	20	20	20	18	18
Agar-agar.....			2	..	..	..	..	..	..
McCullum's salts 185.....			4	4	4	4	4	4	4
Butter fat.....			5	10	5	5	5	10	8
Northwestern yeast.....			..	..	10	..	..	..	..
Autoclaved yeast.....			..	..	..	10	5	5	5
Dextrin.....			69	68	61	61	66	..	..
Cod liver oil.....			..	..	..	..	..	..	2
Corn starch.....			..	..	..	..	..	63	63

\* These rations were supplemented with a liberal supply of cow's milk daily.

† This ration was supplemented with 6 drops of cod liver oil daily to each animal.

§ Purified by extraction for one week with water acidulated with acetic acid.

TABLE 2.—The Effect of Deficiency of the Vitamin B Complex and of Uncomplicated Vitamin B Deficiency on the Amount of Fat in the Livers of Nursing Young of the Albino Rat

Diet	Animals	Range in Ages, Days	Range in Weight, Gm.	Percentage of Cases				
				++++	+++	++	+	None
Deficient in vitamin B complex.	67	18 to 29	20 to 35	7.46	16.42	31.34	38.81	5.97
Deficient in vitamin B.....	80	26 to 41	17 to 30	0	0	0	16.30	83.70
Control, stock diet 1.....	32	18 to 26	20 to 45	0	0	0	40.63	59.37
Control, stock diet 6.....	55	4 to 40	8 to 98	0	0	23.64	34.55	41.81
Control, high yeast diet (1145).	69	19 to 21	25 to 30	0	11.60	11.60	7.24	69.56

TABLE 3.—The Effect of Age on the Weights of Liver and Spleen of Nursing Young and of the Weaned Young of the Albino Rat on Stock Diet 1

	Age, Days	Body Weight, Gm.	Liver		Spleen	
			Weight, Gm.	Percentage of Body Weight	Weight, Gm.	Percentage of Body Weight
Nursing young of mothers on stock diet 1	4 (6)*	8.0	0.4676	5.84	0.0492	0.61
	8 (6)	14.4	0.6069	4.33	0.0788	0.56
	12 (5)	15.4	0.6282	4.08	0.0700	0.45
	15 (12)	23.2	0.8769	3.78	.....	...
	16 (12)	21.0	0.8615	4.12	0.0712†	0.38†
	19 (4)	30.0	1.4675	4.89	0.0845	0.28
	24 (5)	33.2	1.7293	5.20	0.1183	0.36
	28 (6)	47.5	3.3173	6.98	0.1090	0.41
Weaned young on stock diet 1	31 (6)	50	4.1203	6.08	0.2188	0.37
	36 (6)	75	5.6120	7.48	0.3232	0.43
	40 (8)	77	5.2304	6.79	0.2949	0.38

\* Numbers in parentheses refer to numbers of animals taken for that particular age.

† The figures for the spleen weights are the average of six nurslings.

TABLE 4.—*The Effect of Deficiency of the Vitamin B Complex and of Uncomplicated Vitamin B Deficiency on the Weights of Liver and Spleen of Nursing Young of the Albino Rat*

	Age, Days	Body Weight, Gm.	Liver		Spleen	
			Weight, Gm.	Percentage of Body Weight	Weight, Gm.	Percentage of Body Weight
Deficiency of vitamin B complex	16 (6)*	12.0	0.4577	3.81	.....	....
	17 (5)	15.0	0.5848	3.90	0.0259	0.17
	19 (4)	24.0	1.4040	5.83	0.0538	0.22
	22 (6)	16.3	0.9291	5.70	0.0308	0.19
	24 (6)	20.0	1.4920	7.46	.....	....
	30 (6)	19.0	1.1172	6.40	.....	....
Uncomplicated vitamin B deficiency	26 (12)	24.5	1.1658	4.34	0.0666	0.27
	28 (6)	21.0	1.2196	5.80	0.0432	0.20
	33 (2)	23.0	1.4813	6.44	0.0370	0.16
	35 (6)	27.5	2.2647	8.23	0.0611	0.22
	41 (5)	24.0	1.6343	6.81	.....	....

\* Numbers in parentheses refer to numbers of animals taken for that particular age.

TABLE 5.—*Comparison of Weights of Adrenal Glands, Spleen, Heart and Liver of the Weaned Albino Rat During a Period of Growth on Control Diets, with Those of the Albino Rat During a Period of Deficiency of the Vitamin B Complex and During a Period of Uncomplicated Deficiency of Vitamin B*

Diet	Age, Days	Animals	Body Wt., Gm.	Adrenals		Spleen		Heart		Liver	
				Weight, Gm.	Per Cent	Weight, Gm.	Per Cent	Weight, Gm.	Per Cent	Weight, Gm.	Per Cent
Control diets: ration 1452 plus from 30 to 150 mg. of an alcoholic extract from yeast foam daily	136	3	164	0.0263	0.016	0.6335	0.38	0.7139	0.43	6.81	4.15
	142	2	162	0.0259	0.016	0.3528	0.22	0.6707	0.41	6.85	4.22
	148	3	186	0.0223	0.012	0.4322	0.23	0.7245	0.39	7.57	4.07
Stock diet 6	92	3	201	0.0185	0.009	0.9403	0.46	0.8441	0.45	8.6000	4.27
	97	4	194	0.0211	0.011	0.8873	0.46	0.8625	0.43	8.4914	4.34
	110	6	204	0.0254	0.012	0.7870	0.38	0.8504	0.41	9.4756	4.63
	118	7	196	0.0253	0.013	0.6358	0.33	0.8168	0.42	9.2800	4.73
Diet deficient in the vitamin B complex: ration 1009	70	2	58	0.0196	0.033	0.1937	0.33	0.3680	0.63	2.6757	4.61
	71	1	47	0.0150	0.032	0.1252	0.27	0.3254	0.68	1.0580	2.23
	73	2	60	0.0269	0.045	0.1775	0.29	0.4609	0.76	3.4435	5.74
	76	2	57	0.0229	0.040	0.1575	0.21	0.4560	0.80	2.5411	4.45
	78	1	56	0.0261	0.046	0.1928	0.34	0.3254	0.58	2.4420	4.36
	87	2	60	0.0198	0.033	0.1283	0.21	0.5105	0.85	4.4405	7.34
	89	2	67	0.0134	0.020	0.1319	0.19	0.4828	0.72	3.1057	4.63
	95	3	67	0.0136	0.020	0.1787	0.26	0.4254	0.63	3.0487	4.55
Uncomplicated vitamin B deficiency: ration 1452 supplemented daily with from 5 to 10 mg. of vita- min B con- centrate 82	78	7	64	0.0174	0.027	0.1726	0.27	0.4279	0.68	3.0190	4.72
	82	5	76	0.0161	0.021	0.1738	0.23	0.5076	0.67	3.2372	4.26
	94	2	62	0.0232	0.037	0.1610	0.26	0.3612	0.58	3.7129	5.98
	99	1	53	0.0218	0.041	0.2155	0.41	0.4016	0.76	3.5049	6.78
	122	1	88	0.0272	0.031	0.1967	0.22	0.3989	0.45	5.9490	6.75
	127	1	88	0.0186	0.021	0.1649	0.19	0.5906	0.67	4.6400	5.27
	134	1	74	0.0210	0.029	0.1760	0.24	0.5380	0.73	3.6850	4.94
	142	2	108	0.0315	0.029	0.2955	0.27	0.5145	0.47	4.5277	4.19

## PATHOLOGIC CHANGES IN NURSING YOUNG OF THE ALBINO RAT

*Deficiency of the Vitamin B Complex.*—Deficiency of the vitamin B complex was produced in the nursing young of the albino rat by a method previously developed by one of us (B. S.<sup>12</sup>), using ration 1009<sup>13</sup> supplemented with enough of the vitamin B complex for maternal welfare, but not for lactation. On such a dietary, nurslings manifested first a cessation of growth, followed by posterior paralysis, which later, unless vitamin therapy was readily instituted, became general, so that it extended to the center of deglutition. Frequently the young developed spasms accompanied by shrills and running fits. They became so tense as to bite the screens of the cage so that they bled from the mouth. It was a rather surprising coincidence that the mothers

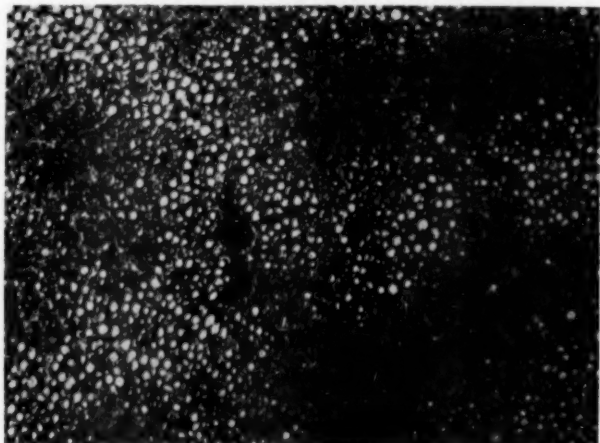


Fig. 1.—Photomicrograph of liver of a nursling of an albino rat suffering from a deficiency of the vitamin B complex; it shows marked vacuolation indicating fatty metamorphosis around the central vein. The weight of the young rat was 29 Gm. and its age 27 days.

stored vitamin in the tissues on the dietary referred to when the young were dying or struggling for independence. Since the young were found dying with their stomachs full of curdled milk, the conclusion drawn was that the derangement must be associated with poor quality rather than with insufficient quantity of milk.<sup>7</sup> In addition to hemorrhages of bones, the most noteworthy observation that we made in this investigation was that such nurslings showed marked fatty metamorphosis of the liver. This is illustrated in figure 1. For this study we employed sixty-seven young rats, from 18 to 29 days of age, and

12. Sure: J. Biol. Chem. **76**:685, 1928.

13. The composition of this ration, as well as those of other rations, is given in table 1.

ranging in weight from 20 to 35 Gm. Some of the tissues were preserved in formaldehyde and stained with eosin and Delafield's hematoxylin or eosin and iron hematoxylin. Numerous sections were frozen and stained with sudan III. Comparisons were made with groups fed three different types of control diets. It is apparent from table 2 that, although on control stock diet 6 and on control diet 1145 an appreciable amount of deposit of fat in livers was observed, the ration deficient in the vitamin B complex produced the most marked fat deposits. Since the majority of the nurslings suffering from deficiency of vitamin B complex (table 4) compared with controls (table 3) had an increase in the weight of the liver in proportion to the body weight, the marked vacuolation observed around the central vein (fig. 1) and also in the periphery of the hepatic lobule is indicative of fatty infiltration. An analysis of tables 3 and 4 also discloses that nurslings deprived of optimum amounts of the vitamin B complex had atrophy of the spleen.

*Uncomplicated Vitamin B Deficiency.*—For this investigation eighty nurslings were used. The uncomplicated avitaminosis was produced in nursing young of the albino rat on maternal diet 1145, supplying an adequacy of vitamin G, but an inadequacy of vitamin B.<sup>8</sup> Employing such biologic technic, we first encountered prolonged maintenance of the nursing young. Eventually they presented posterior paralysis, labored respiration and cyanosis, and finally, unless vitamin B therapy was instituted, death ensued.

Previous work had demonstrated that in young rats suffering from this avitaminosis, hypoglycemia and anhydremia associated with hematopoietic disturbance develop.<sup>14</sup>

Such young had no noteworthy fatty changes in the liver, although there was an increase in the weight of the liver (calculated as percentage of body weight) (table 4) compared with young on the control diets (table 3). Such young, however, had atrophy of the spleen. The most pronounced biochemical change noted in nurslings suffering from uncomplicated vitamin B deficiency was the marked reduction in the glycogen content of the liver. In twenty-nine control animals, the liver glycogen expressed in milligrams of dextrose per hundred grams of liver was from 7.02 to 14.98, while in the vitamin B deficient animals the range of this constituent was from 0.12 to 2.53 mg.<sup>15</sup> No noteworthy changes were found in the rest of the tissues, with the exception of, in a few animals, interstitial pancreatitis and ulcers of the stomach.

14. Sure and Smith (footnote 9).

15. These observations were made by Margaret Elizabeth Smith of the Department of Home Economics.

## PATHOLOGIC CHANGES IN THE WEANED ALBINO RAT

*Deficiency of the Vitamin B Complex.*—For this study, we employed fifteen animals. The deficiency was produced by feeding rations 1009 and 1654. Comparisons were made with twenty-eight animals fed two types of control diets, 1 and 6 (table 1). The period of observation ranged from thirty-five to fifty-seven days, during which there occurred a loss of weight in each animal of from 12 to 29 Gm. The main pathologic changes observed were those associated with inanition, with the exception of hypertrophy of the adrenal glands and the heart (table 5), and fatty metamorphosis of the liver in some animals without the accompanying increase in the weight of the liver. Since all the organs were weighed quickly to prevent evaporation, the hearts were weighed with considerable amounts of blood, and it is possible that the increased weights of the hearts of animals deprived of the vitamin B complex were due to the increased blood flow through that organ, as found by Simonds and Brandes<sup>16</sup> in experimental hyperthyroidism in the dog. At least, our observations on the hypertrophy of the adrenal glands and heart of the albino rat suffering from a deficiency of the vitamin B complex are in agreement with the recent observations of McCarrison and that of Sundarajan in beriberi columbarum.<sup>5</sup>

*Uncomplicated Vitamin B Deficiency.*—In the early part of 1926, Smith and Hendrick<sup>1</sup> demonstrated the dual nature of the vitamin B complex. They reported that rolled oats is not deficient in vitamin B but in another factor which is present in brewer's yeast, and which withstands autoclaving for six hours at 15 pounds (6.8 Kg.) of pressure. Simultaneously with the publication of the work of Smith and Hendrick appeared the paper of Goldberger, Wheeler, Lillie and Rogers<sup>1</sup> in which they established the existence of two vitamins associated with the vitamin B complex. The results of the latter investigators have been since confirmed by Chick and Roscoe,<sup>1</sup> Salmon, Hays and Guerrant,<sup>1</sup> Sherman and Axtmayer<sup>1</sup> and others. The procedure of furnishing the stable antipellagric factor, vitamin G, has now been generally adopted by the introduction of autoclaved yeast. For our work, we used as a source of vitamin G a baker's dried yeast secured from the Northwestern Yeast Company, Chicago, which we autoclaved for six hours in shallow glass pyrex dishes, about 75 mm. deep, at from 15 to 18 pounds (6.8 to 8.2 Kg.) pressure.

Uncomplicated vitamin B deficiency was produced in fourteen weaned albino rats by feeding ration 1676. The period of observation ranged between 39 and 66 days, during which the average loss of weight was 22 Gm. Since on this ration, in the majority of animals, loss of weight

16. Simonds and Brandes: The Effect of Experimental Hyperthyroidism and of Inanition on the Heart, Liver and Kidneys, Arch. Path. 9:445, 1930.

was encountered as early as the second week, accompanied by inanition, an attempt was made to prolong the period of vitamin B deficiency by furnishing daily small amounts of a vitamin B extract used previously in our work<sup>8</sup> which would facilitate the production of prolonged maintenance, and thus circumvent the associated phenomenon of starvation. Similar cases accompanied by small gains of body weight due to an inadequate supply of vitamin B were encountered in animals fed ration 1452 fortified with daily amounts of from 5 to 10 mg. of our vitamin B concentrate 82. On the latter dietary regimen we employed fifteen animals, the experimental period lasting for from 61 to 121 days. The average gain in weight of each animal was 12.6 Gm. during an average period of 86 days.

An examination of the results in rats fed a ration deficient in vitamin B, compared with the results in control animals (table 5) indicates that in uncomplicated vitamin B deficiency the adrenal glands weighed considerably more in proportion to the rest of the body weight. This was also true of the heart. In the heart, however, we determined that the increase in weight was due mainly to additional volumes of blood. These results, it will be noted, were observed in animals the condition of which was uncomplicated by the phenomenon of starvation, since they were on ration 1452 supplemented with small amounts of a vitamin B extract, which allowed even small gains in weight.

The gross pathologic changes observed in the animals on ration 1676, in which loss of weight was produced, accompanied by inanition, were emaciation, marked dilatation of the stomach with undigested food, hypertrophy of the adrenal glands and heart and atrophy of the spleen.

**Microscopic Changes in Uncomplicated Vitamin B. Deficiency:** The heart, stained with sudan IV, revealed no fat, except that normally present in the pericardium.

The spleen showed atrophy, as diagnosed by decrease in parenchymal structures with connective tissue replacement. Hemosiderin was present to a great extent.

The gastro-intestinal tract was normal, except for a small ulcer in one stomach. Our histologic observations on the gastro-intestinal tract were essentially in agreement with those of Findlay. This investigator studied, in addition, mitochondria of the cells of the stomach and intestines. He reported that "in the chief cells of the stomach and in the cells of the glands of Lieberkühn there was some transformation of the rod-like mitochondria into granules."<sup>6</sup>

No study was made of the peripheral nervous system.

The liver presented no apparent change, except a slight amount of fatty changes irregularly distributed in fine droplets, in one animal. Three sections indicated focal necrosis.

The thymus showed atrophy, as indicated by connective tissue replacement.

No noteworthy histologic changes were present in the lungs, aorta, kidneys, salivary glands, thyroid gland, tongue or pancreas.

#### VITAMIN B, GROWTH AND FOOD INTAKE

It has been generally assumed that beneficial effects of vitamin B on growth and general well-being result indirectly through increase of food consumption, since the administration of vitamin B, which is generally given in liberal amounts, is always accompanied by an increase of appetite. During the last two years we had occasion to test in the laboratory vitamin B concentrates prepared by one of us (B. S.) by the Sherman method of biologic assay.<sup>17</sup> This method consists in feeding daily to weaned litter mates (experimental rats) graduated amounts of materials containing vitamin B as a supplement to, and separately from, a diet satisfactory except for vitamin B; an average gain of approximately 3 Gm. per week per rat for a period of eight weeks was noted. One of the vitamin B concentrates recently developed for human application is so potent that 0.7 mg. daily produces this desired amount of growth. This vitamin B extract we have designated as concentrate 89. Two animals of the same litter, which received the basal ration without any supplement of vitamin B (the negative controls) consumed as much food as two comparable litter mates receiving the vitamin extract, but the different results in growth were striking. For instance, ♀ 6597, negative control, ate 139 Gm. during the experimental period and lost 21 Gm.; ♀ 6593, which received a daily supplement of from 0.4 to 0.7 mg. of vitamin B concentrate 89, and consumed 140 Gm., gained 14 Gm. Also, ♀ 6596, which received a daily supplement of from 0.4 to 0.9 mg. of the same vitamin extract and ate 137 Gm., lost 11 Gm. less than the control litter mate, ♀ 6597, on comparable food intake. The second control, ♂ 6598, ate 224 Gm. and gained 2 Gm., while ♂ 6594, the litter mate on comparable food consumption (228 Gm.) with vitamin B supplement, gained 18 Gm., while the last litter mate, ♂ 6595, with a food intake of even 18 Gm. less (210 Gm.) than the litter mate control, gained 46 Gm. These results, obtained in animals receiving small amounts of vitamin B supplements for slow growth, conclusively demonstrate the specific effect of vitamin B per se on growth, unrelated to food intake.

17. Sherman: Food and Nutrition, New York, The Macmillan Company, ed. 3, 1927, p. 308.

THE EFFECT OF UNCOMPLICATED VITAMIN B DEFICIENCY ON THE  
TOTAL AND DIFFERENTIAL LEUKOCYTE COUNT

In 1921, Cramer, Drew and Mottram<sup>18</sup> reported that a diet deficient in vitamin B resulted in atrophy of lymphoid tissue throughout the body and in lymphopenia in the circulating blood of mice and rats. In 1922, Happ<sup>19</sup> observed leukopenia in the rat suffering from vitamin B deficiency. Recently, Sure, Kik and Walker<sup>20</sup> could find no appreciable change in the total leukocyte count in albino rats on a dietary deficient in the vitamin B complex.

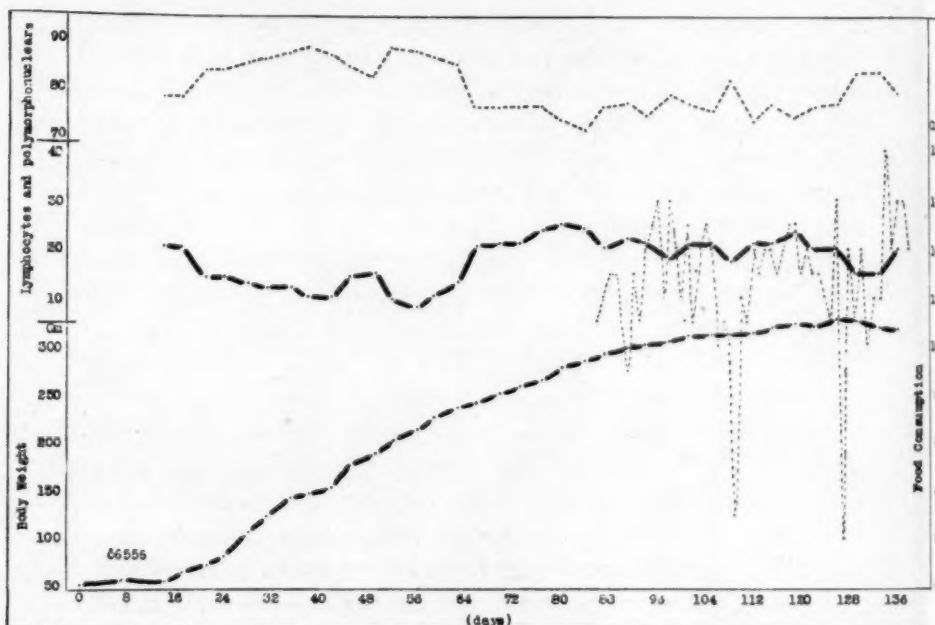


Fig. 2.—Total lymphocyte and polymorphonuclear counts on ration 1202. The upper curve in dotted lines represents total lymphocytes in per cent; the middle curve in heavy lines, total polymorphonuclear leukocytes in per cent; the lower curve in dotted lines, food consumption in grams, and the lower curve in heavy lines, body weight in grams.

In this investigation, a study was made of the total and differential count in eighteen albino rats suffering from uncomplicated vitamin B deficiency. The avitaminosis was produced on a dietary described in the second paper of this series.<sup>21</sup> The animals were taken in groups of six,

18. Cramer; Drew, and Mottram: *Lancet* **1**:963, 1921; *ibid.* **2**:1202, 1921; *Proc. Roy. Soc. London* **93**:449, 1922.

19. Happ: *Bull. Johns Hopkins Hosp.* **33**:163, 1923.

20. Sure; Kik, and Walker. *J. Biol. Chem.* **83**:387, 1929.

21. Thatcher; Sure, and Walker: *Avitaminosis: II. Pathologic Changes in the Albino Rat Suffering from Vitamin G Deficiency*, *Arch. Path.*, this issue, p. 425.

which were litter mates; the fifth and sixth animals were controls, which were given our ration 1202 containing 5 per cent of untreated dehydrated baker's yeast as a source of vitamins B and G. The total leukocyte and differential counts were made twice weekly, peripheral blood from the tail being used according to the technic of Hart and his co-workers.<sup>22</sup> Wright's stain was used for the differential count. No attempt was made to distinguish the small from the large lymphocytes, both being included under the total lymphocyte count. Typical illustrations of our results are presented in figures 2 and 3. No noteworthy change in the total leukocyte count was found in this avitaminosis.

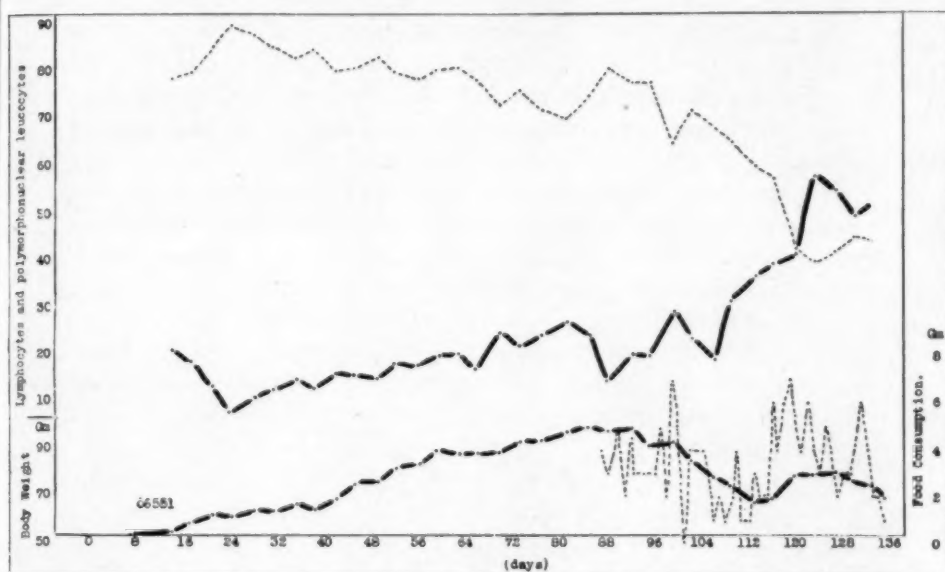


Fig. 3.—The effect of vitamin B deficiency on the total lymphocyte and polymorphonuclear leukocyte counts. The upper curve in dotted lines represents total lymphocytes in per cent; the middle curve in heavy lines, total polymorphonuclear leukocytes in per cent; the lower curve in dotted lines, food consumption in grams, and the lower curve in heavy lines, body weight in grams.

There was, however, a pronounced effect on the polymorphonuclear-lymphocyte ratio, the lymphocytes being markedly reduced, with a corresponding increase in the polymorphonuclears. In the control animals, age and increase of body weight did not produce any appreciable change in the distribution of either the polymorphonuclears or the lymphocytes. Uncomplicated vitamin B deficiency produced no effect on the monocytes, eosinophils or basophils.

22. Hart; Steenbock; Elvehjem, and Waddell: *J. Biol. Chem.* **65**:67, 1925.

Since in vitamin B deficiency the phenomenon of anorexia is always encountered, the question arises: Is the disturbance in the polymorphonuclear-lymphocyte ratio an expression of inanition? It is apparent, however, from the illustration given in figure 3 that, while there is a considerable reduction in food intake, the lymphopenia and corresponding polymorphonuclear leukocytosis are observed during periods when there is an intake of appreciable amounts of food. At least, the disturbance in the differential count is not due to starvation; a lack of an optimum food intake may, however, be a contributing factor.

#### SUMMARY

Nursing young of the albino rat suffering from a deficiency of the vitamin B complex show fatty metamorphosis of the liver. Such young also have atrophy of the spleen, as well as hemorrhages in osteogenic tissues and anhydremia associated with disturbance in hematopoietic function.

Nursing young of the albino rat suffering from uncomplicated vitamin B deficiency have marked reduction in the glycogen content of the liver and atrophy of the spleen, as well as hypoglycemia and anhydremia associated with hematopoietic disturbance.

The pathologic changes observed in weaned albino rats deprived of the vitamin B complex are mainly those associated with inanition. In addition, hypertrophy of the adrenal glands and of the heart has been noted. Fatty metamorphosis of the liver has also been observed in some animals.

Observations on weaned albino rats suffering from uncomplicated vitamin B deficiency have been made on two groups of animals: (1) those entirely deprived of vitamin B and (2) those securing daily amounts of vitamin B inadequate for optimum growth and welfare. Atrophy of the spleen and hypertrophy of the adrenal glands and heart (in the latter organ mainly due to increased blood volume) were the changes noted, but the significance of these observations is that they were noted on animals of group 2 that showed even a slight gain in body weight and, therefore, were uncomplicated by inanition.

Vitamin B *per se* possesses the function of producing growth unrelated to food intake.

Uncomplicated vitamin B deficiency in the albino rat produces lymphopenia and a corresponding polymorphonuclear leukocytosis.

## AVITAMINOSIS

### II. PATHOLOGIC CHANGES IN THE ALBINO RAT SUFFERING FROM VITAMIN G DEFICIENCY \*

HARVEY S. THATCHER, M.D.

LITTLE ROCK, ARK.

AND

BARNETT SURE, Ph.D.

AND

DOROTHY J. WALKER, M.S.

FAYETTEVILLE, ARK.

In February, 1926, Goldberger, Wheeler, Lillie and Rogers <sup>1</sup> demonstrated the dual nature of the dietary essential, vitamin B. The differentiation was made mainly on the basis of thermostability. In May, 1926, Goldberger and Lillie <sup>2</sup> produced evidence that a deficiency of the stable factor in a diet fortified with an abundance of the labile, antineuritic vitamin resulted in a pellagra-like disease in the rat. Following the arrest of growth, alopecia, bilateral symmetrical lesions of the skin, stomatitis and ophthalmia were noted. The conclusion the authors made was that it is probable that the pellagra-like condition in the rat may be the analogue of pellagra in man, but that additional evidence is necessary to establish this fact. It may be pointed out that this is the first time since 1913-1914, when McCollum and Davis <sup>3</sup> and Osborne and Mandel <sup>4</sup> described a lesion of the eye in vitamin A deficiency, that ophthalmia has been found associated with a dietary deficiency, and that it would therefore be erroneous in the future to designate vitamin A as the antiophthalmic vitamin, as has been done in the past. The "saltophthalmia" reported in 1922 by McCollum, Simmonds and Becker <sup>5</sup> was later found by Simmonds, Becker and McCollum <sup>6</sup> to be due to a deficiency in vitamin A rather than to a mineral deficiency.

---

\* Submitted for publication, July 21, 1930.

\* Research paper no. 146, Journal Series, University of Arkansas.

\* From the Department of Medical Pathology of the University of Arkansas, Little Rock, and the Department of Agricultural Chemistry, of the University of Arkansas, Fayetteville.

1. Goldberger; Wheeler; Lillie, and Rogers: Pub. Health Rep. **41**:297, 1926.

2. Goldberger and Lillie: Pub. Health Rep. **41**:1025, 1926.

3. McCollum and Davis: J. Biol. Chem. **15**:167, 1913; *ibid.* **19**:245, 1914.

4. Osborne and Mendel: J. Biol. Chem. **16**:423, 1913-1914.

5. McCollum; Simmonds, and Becker: J. Biol. Chem. **53**:313, 1922; *ibid.* **64**:161, 1925.

6. Simmonds; Becker, and McCollum: J. Nutrition **1**:39, 1929.

In 1927, Chick and Roscoe<sup>7</sup> corroborated the main observations of Goldberger and Lillie,<sup>2</sup> designating the stable factor as B<sub>2</sub> according to the English nomenclature. They suggested that they might be dealing with more than one dietary deficiency, for animals occasionally deprived of B<sub>2</sub> remained stunted in growth, but exhibited no special lesions of the skin.

In 1928, Salmon, Guerrant and Hays<sup>8</sup> confirmed the work of Goldberger and Lillie, but in addition reported the presence of a gram-positive coccus, which they obtained from skin and arthritic lesions, parenchymatous organs and the walls of the intestines.

Recently Chick and Roscoe<sup>9</sup> demonstrated that the so-called antipellagric factor is unstable at temperatures of from 122 to 125 C. in an alkaline medium.

In March, 1929, Sherman and Sandels<sup>10</sup> described their experiences with vitamin G deficiency in the albino rat. Their observations were similar to those reported by Goldberger and Lillie<sup>2</sup> and by Chick and Roscoe.<sup>9</sup>

After the completion of our investigation, the results of which are submitted in this communication and a preliminary report of which appeared recently,<sup>11</sup> the work of Findlay<sup>12</sup> published in 1928 came to our attention. Our observations conform to a great extent to his, further reference to which will be made later in the paper.

#### RATIONS EMPLOYED

Table 1 gives the composition of the rations employed in this study. Ration 1522 is a duplicate of the one reported by Hunt,<sup>13</sup> abundant in vitamin B, but extremely deficient in vitamin G (according to this investigator) from the standpoint of growth. Ration 1521 is a duplicate of ration 1522 slightly modified to reduce the salt content from 5 to 4 per cent. In an effort to construct satisfactory diets for the development of vitamin G deficiency, it was anticipated that our method of freeing casein from the vitamin B complex, which consists in extraction for one week with acidulated water, might be inadequate for the complete removal of the stable factor. In a number of experiments we therefore used casein that had been extracted with 60 per cent alcohol according to the method of Sherman and Spohn<sup>14</sup> subsequent to extraction with acidulated water (ration 1654-b). The method of preparation of the vitamin B supplement furnished by

7. Chick and Roscoe: *Biochem. J.* **21**:698, 1927; *ibid.* **22**:790, 1928.

8. Salmon; Guerrant, and Hays: *Etiology of Dermatitis of Experimental Pellagra in Rats*, *J. Infect. Dis.* **43**:426, 1928.

9. Chick and Roscoe: *Biochem. J.* **24**:105, 1930.

10. Sherman and Sandels: *Proc. Soc. Exper. Biol. & Med.* **26**:536, 1929.

11. Thatcher; Sure, and Walker: *South. M. J.* **23**:143, 1930.

12. Findlay: *J. Path. & Bact.* **31**:353, 1928.

13. Hunt: *J. Biol. Chem.* **78**:83, 1928.

14. Sherman and Spohn: *J. Am. Chem. Soc.* **45**:2719, 1923.

an alcoholic extract from dried baker's yeast was that described by Sherman and Sandels.<sup>10</sup> In ration 1654-c we used casein that had been irradiated for ten hours with a mercury quartz vapor lamp (after extraction with acidulated water), following the suggestion of Hogan and Hunter<sup>15</sup> that such treatment destroys vitamin G, but leaves vitamin B intact. The latter idea was also introduced in the development of the following dietary, which was found the optimum (from the months of April to September, 1929) for the production of vitamin G deficiency accompanied by dermatitis. Rations 1640 and 1692 were supplemented as described in table 1 with from 300 to 500 mg. of rice polishings that had been irradiated for ten hours with a mercury quartz vapor lamp, as a source of vitamin B. Irradiating the casein of the rations seemed to expedite the onset of dermatitis in those animals in which the skin lesions developed. Ration 1641 is our ration 1009<sup>16</sup> deficient in the vitamin B complex and supplemented with from 30 to 60 mg. daily of vitamin B concentrate 82 (used previously in studies on the biochemistry of avitaminosis,<sup>17</sup> which furnishes an abundance of vitamin B, but an inadequate amount of vitamin G, for optimum growth and welfare.

TABLE 1.—Composition of Rations

Dietary Components	Ration							
	1521	1522	1640†	1641‡	1692#	1654-a	1654-b	1654-c
Casein*	20	18	20	20	18	..	..	18
Casein‡	..	..	..	..	..	18	..	..
Casein§	..	..	..	..	..	..	18	..
Corn meal	25	25	..	..	..	..	..	..
McCullum's salts no. 185	4	5	4	4	4	4	4	4
Cod liver oil	2	2	..	..	..	..	..	..
Butter fat	..	..	5	5	10	10	10	10
Crisco	10	10	..	..	..	..	..	..
Starch	39	40	..	..	..	..	..	..
Agar-agar	..	..	2	2	..	..	..	..
Dextrin	..	..	60	60	68	68	68	68

\* Purified by extraction for one week with water acidulated with acetic acid.

‡ Purified by extraction with 60 per cent alcohol.

§ Irradiated for ten hours with a mercury quartz vapor lamp.

† This ration was supplemented as follows: six drops of cod liver oil was administered to each animal daily; 100 mg. of an alcoholic extract from yeast was given for from forty to fifty days until growth ceased; then the administration of this preparation was replaced by that of 500 mg. of rice polishings, irradiated for ten hours, daily to each animal, as a source of vitamin B.

‡ This ration was supplemented by the administration of 6 drops of cod liver oil and from 30 to 60 mg. of vitamin B concentrate 82 (an extract from rice polishings) daily to each animal.

# On the twenty-first day after the initiation of the experiment, the ration was supplemented with from 300 to 500 mg. of rice polishings, irradiated for ten hours with a mercury quartz vapor lamp.

|| After the animals had depleted their reserves of the vitamin B complex, this ration was supplemented with from 100 to 200 mg. daily of an alcoholic extract from baker's yeast.

#### GENERAL OBSERVATIONS

A summary of our observations on the symptomatology of vitamin G deficiency is presented in table 2. Sixty-four animals were studied on the different vitamin G-deficient rations. Comparisons were made with twelve animals on ration 1,452 (table 1) containing autoclaved

15. Hogan and Hunter: J. Biol. Chem. **78**:433, 1928.

16. Sure: J. Biol. Chem. **76**:673, 1928.

17. Sure and Smith: J. Nutrition **1**:537, 1929.

TABLE 2.—Pathologic Symptoms Observed in the Albino Rat on Rations Deficient in Vitamin G

Ration	Animal	Duration of Experiment, Days	Change of Weight During Experiment, Gm.	Period After Which Growth Ceased, Days	Dermatitis, Period of Onset, Days	Ophthalmia, Period of Onset, Days	Chromogenic, Urine, Period of Onset, Days	Incontinence of Urine, Period of Onset, Days
1521	♀ 6136	140	+17	84	...	...	...	...
	♀ 6137	140	+26	69	120	34	72	34
	♂ 6138*	140	+55	115	106†	...	...	...
	♂ 6139‡	140	+35	84	...	...	...	...
	♂ 6140*	140	+20	86	83	80	...	...
	♂ 6141*	87	+1	86	...	54	41	...
1522	♀ 6142	133	+29	69	...	...	...	...
	♀ 6143‡	121	+24	69	...	...	...	...
	♀ 6144	92	+22	46	...	...	...	...
	♀ 6145	92	+13	50	...	...	75	75
	♂ 6146	127	+35	62	89	...	...	...
	♂ 6147*	95	+20	58	61	...	...	...
1640	♂ 5052	189	+85	146	85‡	...	42‡	...
	♀ 5053	98	+22	83	28‡	33‡	36‡	36‡
	♀ 5060	132	+20	96	48‡	...	...	...
	♀ 5061	139	± 0	96	48‡	...	...	...
	♀ 5062	117	+40	94	37‡	...	...	...
	♀ 5063	151	+16	108	66‡	25‡	35‡	...
1692	♀ 6124	104	+42	98	...	...	...	...
	♀ 6125	104	+74	98	...	...	...	...
	♀ 6126	147	+102	146	93‡	...	...	...
	♂ 6127‡	121	— 6	86	34‡	...	34‡	...
	♂ 6128	147	+65	99	80‡	...	50‡	...
	♂ 6129	147	+71	146	...	...	50‡	...
1641	♀ 5054	147	+117	147	...	...	...	...
	♀ 5055	147	+67	139	...	...	...	...
	♀ 5056	91	+60	83	52	56	...	...
	♂ 5058	132	+31	109	127	...	114	127
	♂ 5059	147	+81	108	...	...	...	...
	♀ 5064	147	+64	105	...	...	...	...
	♀ 5065	76	+18	48	...	...	...	...
	♀ 5066	153	+31	108	107	151	91	91
	♂ 5067	76	+4	69	...	...	75	75
	♂ 5069	77	+56	94	70	76	...	...
1654-a	♀ 6016	132	+85	110	...	...	...	...
	♀ 6017	62	— 9	1	...	...	...	...
	♀ 6018	175	+11	88	131	171	...	...
	♂ 6019	143	+6	77	131	...	82	124
	♂ 6020	62	— 4	14	...	...	...	...
	♂ 6021	62	— 4	14	...	...	...	...
1654-b	♀ 6024	62	— 5	1	...	...	...	...
	♀ 6025	62	—11	1	...	...	...	...
	♀ 6026	71	— 6	1	...	...	...	...
	♂ 6027	97	+4	75	...	...	...	...
	♀ 6022‡	42	— 1	9	...	...	...	...
	♂ 6023	61	—11	1	...	...	...	...
1654-c	♀ 6028	65	—17	7	...	...	...	...
	♀ 6029	65	—11	1	...	...	...	...
	♂ 6030	114	+40	108	102	...	...	...
	♀ 6031	114	+42	111	84	...	86	...
	♀ 6032	62	— 3	14	...	...	...	...
	♀ 6033	62	—11	1	...	...	...	...
	♀ 6080**	114	+6	90	98	...	...	...
	♀ 6081**	122	+35	122	...	...	...	...
1641	♀ 6078	73	+6	70	...	...	...	...
	♀ 6079	73	+3	71	...	...	...	...
	♀ 6082	70	+30	70	29	...	61	61
	♂ 6083	71	— 3	51	29	...	61	61
1654-b††	♂ 6084	70	+6	63	62	...	...	...
	♂ 6085	70	— 8	16	62	...	...	...
	♀ 6086	70	—11	1	...	...	...	...
	♀ 6087	70	— 7	1	...	70	...	...
	♀ 6088	119	+32	91	...	...	...	...
	♀ 6089	119	+44	114	...	...	...	...

♀ indicates female; ♂, male.

\* This rat's ration was supplemented from the twenty-seventh day on with 100 mg. daily of an alcoholic extract from rice polishings, irradiated for ten hours.

† Slight eschars on left upper jaw.

‡ Animal was in dying condition twelve days before termination of experiment; responded to vitamin B therapy.

§ Died; paralyzed on the previous day.

¶ This period is calculated from the time the ration received the first supplement of irradiated rice polishings as a source of vitamin B.

‡ Animal died before autopsy could be made.

\*\* Animal died on forty-second day.

\*\* Changed to ration 1654-b on eighty-first day of experiment.

†† Starch of ration replaced with dextrin.

yeast supplying vitamin G and supplemented with larger dosages of vitamin B concentrates, so that excellent growth was obtained without the accompaniment of any external pathologic changes. Comparisons were also made with twenty animals that showed excellent growth and all the external signs of normality on our stock diet 6 (table 1 in paper 1).

Dermatitis was encountered in twenty-seven of the sixty-four animals examined, or in 42 per cent. The incidence of ophthalmia, however, was only 15 per cent. Ophthalmia sometimes appeared before and sometimes after the dermatitis. It is also apparent from what has already been presented that dermatitis developed, unaccompanied by ophthalmia, in seventeen animals. Such results, as well as our failure to find stomatitis, seem to be contrary to the experience of previous investigators. Chromogenic urine was found in 25 per cent and incontinence of urine in

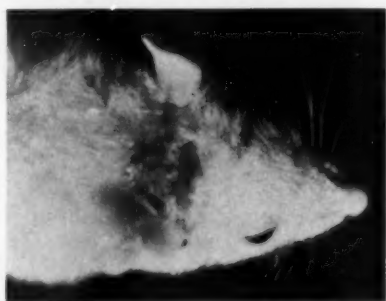


Fig. 1.—Fresh lesions on the head of an albino rat suffering from vitamin G deficiency.

14 per cent, of the animals studied. Priapism was observed in seven, and diarrhea in only two, of the sixty-four animals; therefore, these symptoms are not associated specifically with vitamin G deficiency.

In the construction of the rations, one of the main objectives was to obtain evidence of a correlation between loss of weight and dermatitis. This information is essential if it is to be accepted that vitamin G is an antidermatitic factor and at the same time a growth-promoting dietary essential. Our results, shown in detail in table 2, evidence no such correlation. In fifteen of twenty-seven cases, the dermatitis preceded cessation of growth, while in over 50 per cent of the animals cessation of growth was not accompanied by any lesions of the skin. Such evidence does not justify the conclusion that the antidermatitic and growth-promoting syndromes associated with vitamin G deficiency are identical.

With the exception of the failure of continuous growth and the loss of body weight, dermatitis was the symptom most frequently

observed, 42 per cent of the animals presenting it. The following observations were made on the occurrence of dermatitis: The hair became thin and roughened. In these regions of alopecia, eschars with raised irregular edges appeared suddenly. The eschars averaged from 1 to 4 mm. in their largest dimension. They were brownish red when the bleeding stopped, but later were gray, rough and irregular. When they were removed, there remained a moist, depressed surface. The lesions had a tendency to be bilateral, and they were present mainly on the side and top of the head (fig. 1), on the forepaws, shoulders and



Fig. 2.—Marked hyperkeratosis in the skin of an albino rat suffering from vitamin G deficiency.

jaws and around the eyes. Scratching caused some of the lesions, but we are not certain that it was the cause of all of them.

#### OBSERVATIONS AT AUTOPSY

The animals were killed with ether anesthesia, and complete autopsies were made immediately. Tissues were fixed in Zenker's solution without acetic acid and stained by the Giemsa method. Fixation with solution of formaldehyde and hematoxylin-eosin staining were also used. A general study of the important lesions was made.

*Skin.*—Ulceration was the usual change. These ulcers varied in size and consisted of a varying amount of disintegrated tissue containing

polymorphonuclear leukocytes undergoing degeneration. The deeper layers of the skin were sometimes involved, and the granuloma might extend far into the muscularis. Cells of the lymphocyte series were occasionally present. When the epidermis had disappeared, it was replaced by necrotic material. Hyperkeratosis was present on the sides of the ulcer and also in places in which the epidermis had not disappeared. It was sometimes present with no relation to the ulcer (fig. 2). Parakeratosis also occurred. Desquamation of keratinized material was frequent. Disintegration of the hair follicles, sebaceous glands and elastic fibers was prominent.

*Gastro-Intestinal Tract.*—In several sections of the stomach, eosinophil polymorphonuclear leukocytes and a few cells of the lymphocyte series were more prominent between the glands and in the submucosa of the rumen than in the normal stomach. In one section of the rumen there was an ulcer; in another, there was a small abscess. Congestion of the intestines was almost constant. Hemorrhage was present in the villi to a great extent in the two animals in which hemorrhage was demonstrated grossly. Erosion of the epithelium occurred in the intestines to a slightly greater extent than in the control animals.

No papillomatous proliferation of the squamous epithelium occurred in the stomachs as reported by Findlay,<sup>12</sup> since our animals were on screens, and therefore had no opportunity to scatter hair that was shed.<sup>18</sup>

*Liver.*—Several sections contained fat (sudan IV). This fat was in huge droplets, usually with a tendency to be arranged around the central vein. On our control diets,<sup>19</sup> the liver of the albino rat represented 4.43 per cent of the body weight. On the rations deficient in vitamin G, the liver represented 6.39 per cent of the body weight.<sup>20</sup> Such results would indicate fatty infiltration.

*Heart.*—Numerous sections of the heart muscle contained no fat in fibers (sudan IV). The weights of hearts of the animals showing vitamin G deficiency, compared with controls,<sup>21</sup> indicated cardiac hypertrophy. This, however, as in the case of vitamin B deficiency, may have been due to the increased blood flow in that organ.

*Spleen.*—Atrophy of the spleen was noted by decrease in parenchymal cells, increase in fibrous tissue and decrease in weight of the

18. Pappenheimer and Larimore: J. Exper. Med. **40**:719, 1924.

19. For composition of diets see table 1 in Sure; Thatcher, and Walker: Avitaminosis: I. Pathologic Changes in Nursing and in Weaned Albino Rats Suffering from Vitamin D Deficiency, Arch. Path., this issue, p. 413.

20. These figures represent averages of all the animals under observation.

21. See table 5 of paper I (footnote 19).

organ. The malpighian bodies had almost entirely disappeared, and there was replacement by connective tissue.

*Adrenal Glands.*—An increase in the weight of the adrenals was found, when calculated as percentage of the total body weight.

*Thymus.*—From the sections examined there was involution because of the presence of fat and fibrous tissue.

*Testicles.*—Active spermatogenesis was present.

*Other Observations.*—There were no noteworthy microscopic changes in the brain, thyroid gland, tongue, esophagus, kidneys, skeletal muscle, aorta, salivary glands, pancreas, lungs, ovaries or urinary bladder.

#### COMPARISON OF OBSERVATIONS WITH THOSE MADE IN HUMAN PELLAGRA

The most puzzling point is that, although nine of twelve animals presented dermatitis on rations 1640 and 1692 which were deficient in vitamin G (table 1) during the period from April to September, 1929, only one of eighteen animals presented dermatitis on the same diets from September, 1929, to May, 1930. The other symptoms of vitamin G deficiency mentioned previously were, however, apparent in the warmer, as well as in the colder, months. Such observations seem to be in harmony with experience in human pellagra. Such results have been noted for the first time in the experimental production of vitamin G deficiency in the albino rat. At this writing, we are producing dermatitis successfully on the dietary referred to. As this is an important observation, because of its significance in the symptomatology of human pellagra, more data are being accumulated. MacNeil<sup>22</sup> stated in his article on pellagra "that during the stage of progressive erythema the skin is very sensitive to external irritants, such as sunlight or even contact with the air." Our experimental rats were not exposed to direct sunlight, but they were in a room with an average afternoon temperature of 83 F.

Diarrhea was not a prominent symptom, as it is in many pellagrins. Constipation was also not present. Salivation did not occur as reported by Sherman and Sandels,<sup>10</sup> but this is not important in pellagra. Stomatitis, one of the main symptoms reported by previous investigators, was not present in our rats. Loss of weight was common, and anorexia occurred in some animals in the terminal stages of the avitaminosis. These are frequent symptoms in human pellagra. The presence of ophthalmia and the lack of involvement of the nervous system could not be correlated with the human disease.

22. MacNeil: Am. J. M. Sc. **161**:469, 1921.

Findlay<sup>12</sup> found dermatitis preceding alopecia; vesicles, swollen collagen fibers, atrophy of elastic tissue and congestion of the small blood vessels in the cutis; atrophy of the testicles, and certain lesions of the tongue and the stomach. We were unable to confirm the occurrence of these changes.

The lesions that we observed in the skin were not absolutely comparable with those found in man. Hyperkeratosis and parakeratosis with ulceration occurred, which might have eclipsed the early picture. However, the lesions were bilateral. Rarefaction of the superficial corium, as well as the fibrolytic stage, mitoses and the erythematous change described by Denton<sup>23</sup> as occurring in human pellagra were not observed. Congestion of the intestines is an observation that can be correlated with pellagra. Chromogenic urine and incontinence of urine, observed in some of our animals, are not prominent in human pellagra according to the experience of one of us (H. S. T.) with numerous pellagrins.

In our opinion, neither we nor other investigators preceding us have actually produced a disease in the rat comparable with human pellagra. All that can be said is that pellagra-like symptoms have been experimentally produced. If a true seasonal variation can be established, this might be of considerable importance. Jobling<sup>24</sup> emphasized the fact that sensitization to light may have an important place in the etiology of pellagra. It is possible that his work may have significance in relation to pellagrins suffering from vitamin G deficiency.

#### SUMMARY

Vitamin G deficiency was produced in albino rats on a variety of diets. The main symptoms observed were cessation of growth, loss of weight and dermatitis. Other accompanying symptoms noted in some animals were ophthalmia, chromogenic urine and incontinence of urine. No correlation was found between loss of body weight and the onset of skin lesions, and it is therefore concluded that the antidermatitic and growth-promoting syndromes are not identical. A seasonal variation was noted in the occurrence of the dermatitis.

Alopecia, ulceration of the skin, atrophy of the spleen and of the thymus, fatty changes of the liver and hemorrhages and congestion of the intestines were the main pathologic changes.

23. Denton: *Am. J. Trop. Med.* **5**:173, 1925.

24. Jobling and Arnold: *Etiology of Pellagra*, *J. A. M. A.* **80**:365, 1923.

## General Review

---

### BENZENE (BENZOL) POISONING \*

ALICE HAMILTON, M.D.

BOSTON

This is an attempt to summarize what was published to December, 1930, regarding the action of coal tar benzene,  $C_6H_6$ , on animals and on human beings. The effect of large doses resulting in acute poisoning can be considered fairly briefly; the more important action of small doses administered over long periods of time has been far more extensively studied, and here there are many records of experiments on animals and also of the experimental use of benzene in the treatment for leukemia. There are also a fair number of careful clinical histories of chronic benzene poisoning, always in industrial workers, and a small number of detailed reports of autopsies. In view of the importance and the unusually interesting character of chronic benzene poisoning there is a surprisingly small number of carefully studied clinical cases in the literature, and knowledge of the action of this poison must be gathered in large part from the experimental field.

Benzene, commercially known as benzol, is a colorless, limpid liquid, with a characteristic odor which is rather pleasant. It boils at 80.2 C., has a specific gravity of 0.899 at 0 C., is highly insoluble in water, is somewhat soluble in alcohol, and is an excellent solvent for rubber, gums, resins and fats of all kinds. The industrial uses are based on this solvent action. Pure benzene is not used in industry; the ordinary variety contains some toluene and xylene, perhaps olefins, paraffins, carbon disulphide, etc.<sup>1</sup>

#### ACUTE BENZENE POISONING

Acute benzene poisoning has been the subject of study both experimental and clinical, but not nearly to the extent that has chronic poisoning, for the changes produced are not of so unusual a character. In acute poisoning benzene produces the condition characteristic of the action of an asphyxiating agent. It has a pronounced effect on the central nervous system, causing at first irritation, muscular twitchings, deepening of respirations, which are quickened at first and then slowed, quickening of the pulse rate, lowering of temperature and, in fatal cases,

---

\* Submitted for publication, Jan. 10, 1931.

1. See Final Report of the Committee of the National Safety Council, May, 1926.

narcosis, convulsions and death from paralysis of the respiratory center. The blood remains fluid for a long time after death (Lehmann, Heffter, Sury-Bienz, Beinhauer). Lehmann's animals showed no characteristic changes at autopsy, no odor of benzene and no microscopic changes in the blood. If the lung cavity is opened promptly there may be an odor of benzene.

Kobert (p. 926) classed benzene under the heading, "Poisons Which Can Kill Without Causing Severe Anatomical Changes" and under the subhead "Poisons of the Central Nervous System." He quoted Simpson and Snow as having tested it "decades ago" as an anesthetic; they found that it could not be used for man because of muscular twitchings and other unpleasant symptoms.

Rambousek tested benzene on dogs and rabbits, finding the former more susceptible. No after-effects were noted in those that survived, nor was anything found after death in those dying of the effects, beyond a moderate hyperemia of the brain, lungs and mesenteric vessels.

Benech, in 1878, found that benzene produced glycosuria in guinea-pigs, but not in rabbits or in dogs (Kobert). Beinhauer called it a hemolytic poison, and so did Lewin in the 1897 edition of his "Toxicologie," but Kobert could not bring about the elimination of blood coloring matter in the urine by subcutaneous injection of benzene even in cats, although cats are unusually susceptible to hemolyzing agents.

Schmiedeberg, in 1881, studied the excretion of benzene, and found that when administered by mouth, it is excreted partly in the expired air without change and partly by the kidneys, not as phenol, but in the form of conjugated sulphuric or glycuronic acids. This conjugation of the oxidation products of benzene is a necessary condition for their appearance in the urine.

The earliest record of an autopsy in a case of acute benzene poisoning was published in 1888 by Sury-Bienz. He found conspicuous bright red death spots; the blood was fluid and dark; there were large and small hemorrhages in the pleura and in the intestinal mucosa, general venous congestion, and a reddened lining of the air passages, which contained blood and mucus. The second autopsy did not come until eleven years later, when Beinhauer made one on a man dying of acute benzene poisoning and confirmed every detail of Sury-Bienz's observations, but said in addition that the blood was lake-red, and that there was evidence of destruction of the red blood corpuscles. The body had a curious aromatic odor, but the tests for benzene were negative. The blood was weakly acid.

Even as late as 1907 deaths from acute benzene poisoning were rare enough to require Lewin to write a polemical article, defending his diagnosis of death from benzene vapors in a man who lived only ten minutes after he was rescued from a tank into which benzene was

dripping. Buchmann, in 1911, reported an autopsy with typical results, i. e., wine-red spots on the skin, pronounced hyperemia of the internal organs and small hemorrhages in the pancreas. During the war Martland (1917) examined the bodies of two men who died from acute poisoning in the making of synthetic phenol. One showed cyanosis of the mucous membranes and finger-tips, cyanosis of the liver, spleen and kidneys, dilatation of the right side of the heart, which was filled with dark, fluid blood, pleural ecchymoses and small areas of acute interstitial emphysema in the lungs. The other one had, in addition, cyanosis of the brain, petechial hemorrhages in the pericardium and reddened and irritated bronchi. On section of the lungs a decided odor of benzene was given off. The urine contained an abnormal quantity of phenol, but no benzene.

The presence of phenol bodies in the urine was noted by Heffter and by Beisele and by Simonin, as well as by Martland. Beisele failed to find blood, albumin or hematoporphyrin. Simonin found urobilin, as well as diminished urea and diminished chlorides. In cases that are rapidly fatal, the search for phenol bodies fails, according to Heffter, for the change to conjugated acids is fairly slow.

Heffter, in 1915, reviewed twenty-one reports of cases of acute benzene poisoning from the German literature. The most characteristic change that is noted in animals is also found in man, i. e., dark red blood which remains fluid for a long time, but in which there is no evidence of hemolysis. Hemorrhages, usually punctate, are found in the lungs and pancreas, and in the gastric and intestinal mucous membranes. The abdominal organs show unusual congestion, and there is bloody mucus in the air passages. There are numerous bright red spots on the skin; there is no odor of benzene, and it cannot be detected chemically.<sup>2</sup>

Ziel told of three workmen who were overcome when the ventilation in a rubber sheeting factory was shut off, one of whom died. The body showed very bright red spots, and at autopsy a condition was found like that following suffocation, all the organs being overfull of blood. Ziel quoted Binder as having made similar observations in 1921: dark, fluid blood, edema of the lungs, congestion of all the organs, especially the abdominal ones, and many punctiform hemorrhages on the surface of the brain.

Floret (1926) found at autopsy numerous hemorrhages in the subcutaneous fat tissue, in serous membranes and in almost all the organs, some very large, some microscopic, the large occurring especially in

2. See, however, Martland's case, page 7. Stuelp also found benzene in the brain after death from acute benzene poisoning (*Ztschr. f. Med. Beamte* **32**:297, 1919).

the brain tissue and meninges. The blood was cherry red like that in carbon monoxide poisoning. This man lived fourteen days after an acute intoxication, long enough for severe anemia to develop, with fever, delirium accompanied by muscular twitchings, and cardiac weakness.

The records of a recent autopsy on a victim of acute benzene poisoning were sent to me by Martland. A chemist was found dead in a laboratory where benzene had leaked over the floor from an apparatus for the production of pyramidon. A second man in the same room was still living when found and later recovered. The evidences of asphyxiation at autopsy were as follows: Cyanosis, fluid blood in the right side of the heart, with marked distention, and areas of acute interstitial emphysema in the lungs. All the other organs were normal. This autopsy was made while the body was still warm, before rigor mortis had come on. There was no distinctive odor in the lung cavity, nor in the brain. Parts of the brain, lung, kidney, liver, spleen and stomach were tested for benzene by A. E. Edel, toxicologist of Essex County, and benzene was found in the brain and lungs. The result of a test for methemoglobin in the blood was negative.

Although the usual outcome of acute benzene poisoning is either death within a short time or complete recovery, in a few instances there is evidence of lasting damage from the acute asphyxia. Genhard saw two cases of acute benzene poisoning in a chemical factory in Basel.

The first occurred in a chemist extracting pyramidon with hot benzene. He had a slight attack of dizziness, which did not trouble him much until he went to bed. Then it became intense, with vomiting, recurring whenever he lay down. This lasted for over two days, so that the only bearable position for him was sitting up with the head bowed. He did not recover completely for twelve days, during which he suffered from uncertain gait and weakness of the legs. At the height of his attack there was cyanosis, his breath was aromatic and his pulse rapid and irregular, but there were no other symptoms.

The second case occurred in a weakly boy, aged 18, who after two days' work had severe dizziness, persistent cyanosis, marked weakness, headache, nausea, anxiety, dyspnea and sweating. Catarrh of the upper air passages developed, with slight fever, and eight days later an exanthem appeared over the back. At the end of twelve days he was still unable to walk.

At the same meeting at which Genhard's paper was read, Wyss reported a case of obstinate and intense dizziness following benzene poisoning, inability to stand, disturbed sleep with bad dreams and psychic depression.

Kobert told of a man who was painting the inside of a reservoir with bitumen and crude benzene. He became acutely intoxicated, as if from alcohol, and recovered, but later without any further exposure he developed pleurisy and catarrh of the lung and was never restored to complete health. One of Lewin's patients had an acute attack of

dizziness, a feeling as if he were drunk, pressure in the head, dyspnea, oppression of the heart and, when these symptoms passed over, a blowing heart murmur, yellow pallor and general nervous exhaustion.

The histories of acute benzene poisoning in the literature reveal clearly the great variation in individual susceptibility to this poison, for it happens fairly often that the one who is exposed for the shorter period dies, while the one who is exposed longer and more intensely survives (Lewin).

#### CHRONIC BENZENE POISONING

Much more interesting than the acute form, resulting from a single severe exposure, is chronic benzene poisoning, which has been the subject of much more study both by means of experiments on animals and through clinical observations, supplemented in a minority of the cases by examination of the bodies of the fatally poisoned.

#### EXPERIMENTAL POISONING IN ANIMALS

There is a fairly extensive literature on chronic benzene poisoning produced experimentally in animals. The first experiments of importance seem to be those of Santesson in 1897. Santesson had before him the task of determining the toxic substance in a solvent used by a group of women workers among whom were found nine with purpura hemorrhagica. The literature on coal tar benzene, which at that time and for years afterward was called either benzine or benzol, but practically never benzene, made little, if any, distinction between the coal tar distillate and petroleum benzine. Thus Santesson quoted Korschenewski as saying that both petroleum and coal tar "benzine" were capable of causing hemorrhage, as shown by purpura and hemorrhage in men working in the petroleum fields of Baku, notably in one who died with purpuric spots, bloody expectoration and bloody vomit. At that time it was not known that the oil of Baku is rich in coal tar benzene.

Santesson used rabbits and administered the benzene (1) through the skin by poultice, (2) through the inhalation of vapors and (3) by subcutaneous injection. The method of inhalation was unsuccessful, but the other two methods resulted in death, the third the more quickly. Santesson assumed that the vapors did not count in the death of the poulticed animals because of the failure of those experiments in which vapors only were administered. He obtained the same effects from crude benzene as from pure, but the crude was the more toxic. He called the crude liquid benzine and the pure, distilling at from 80 to 85 C., benzol. Chronic poisoning was characterized by hemorrhages in the pleura, the lungs and the mucous membrane of the stomach and intestines. In animals poisoned through the skin, hyperemia and edema of the subcutaneous tissues showed the passage of benzene through the

skin. The cause of the hemorrhage in organs and mucous membranes, he believed, was not a fatty degeneration of the vascular epithelium, because this was absent in rabbits. He thought that embolism might be the underlying cause. There is no record of any blood counts having been made in these experiments.

Between the epoch-making paper of Santesson and the next milestone, Selling's publications, little experimental work was done, and the most noteworthy contribution adds hardly anything to the picture. This was the work of Langlois and Desbouis, who, in 1907, treated rabbits, guinea-pigs and pigeons with prolonged inhalations of volatile hydrocarbons, the exact nature of which it is impossible to make out with certainty. They spoke of benzol and of moto-naphtha, which apparently had the same effect. Benzol, they defined as a mixture of benzene and toluene. The vapors were administered in two concentrations, namely, 16 cc. and 24 cc. per cubic meter of air. The most conspicuous effect was true polycythemia, marked and constant, in guinea-pigs, pigeons and rabbits—most marked in the first—failing to appear in dogs and cats. This increase in red blood cells consisted in a progressive rise from 5,250,000 to 8,000,000 in forty-five days, if the dose was moderate, and in five days with a heavy dose. Even a single administration of 24 cc. per cubic meter of air for five hours was followed by a rise of 1,000,000 red cells. A fall in the temperature of the body was also noted. The descent of the red cell count described a regular curve, which reached the normal in guinea-pigs in fifteen days. This could not be attributed to concentration of the blood, for the white count was little altered, slightly decreased, if anything, and there was no increased density of the serum; nor was it due to a massing of red blood cells in the peripheral blood, for the heart blood showed the same picture. The increase in hemoglobin was not proportional to the increase in the number of red cells, and no nucleated red cells were found.

The observations of Langlois and Desbouis, especially with regard to polycythemia, were never confirmed. As to their failure to produce leukopenia of any notable degree, it must be said that Selling had the same experience when benzene was administered by inhalation.

Selling's work in the years from 1910 to 1911 established certain facts with regard to the toxicology of benzene which were confirmed by many experimenters following him. His work stands out above that of any other, not only in the clinical, but in the experimental, field. Practically all subsequent students have used his technic and, as a preliminary to the pursuit of their own particular problems, have repeated his experiments and confirmed his results as to the essential features. The most important effect of benzene when given subcutaneously to animals (equal parts of benzene and olive oil were used by Selling) is leukopenia, the

fall in the count of red cells being far less striking. The most important change found postmortem is aplasia of the bone marrow. Selling showed that by means of injections of benzene with olive oil the leukocytes can be diminished in number to the point of almost complete disappearance from the peripheral circulation and that they may afterward rise to the normal level with recovery. This leukopenia reaches an average of 50 per cent at the end of three days and of 75 per cent at the end of four days, with total disappearance some hours before death. Occasionally there is a slight increase in the white count at the outset (Selling reported this in three animals). In the early stage there is an outpouring of large numbers of normal and abnormal leukocytes, of either the large lymphocyte type with large, deeply staining nucleus and narrow basophil protoplasm, or the same cell with an irregular nucleus and varying degrees of basophilia. Myelocytes were seen by Selling in one case only. The white cells fall on an average 2,200 within twenty-four hours after the first injection and 50 per cent after the second. If the experiment is stopped when the white count has reached 40 to 720, the animal dies, sometimes with the same count, sometimes with a lower. Usually after injections of benzene are stopped, there is a preliminary rise of the white count, then a fall, then a slow rise to normal.

The fall in the red cell count is much less striking, unless benzene is administered over a far longer period. In a small percentage the red count shows a rise following the first injection, perhaps still greater after the second, but always after the third it goes back to the original level or falls below. Sometimes the fall comes after the fourth or the fifth, but in other cases the red count remains constant. The average loss at the end of eight days is only 16 per cent, while the loss of white cells averages 92 per cent. But in recovery, while the white cells are returning to normal, the red cells show no similar tendency.

The disappearance of the white cells, according to Selling, is not due to accumulation in other parts of the circulation, because they are absent from the vessels throughout the body.<sup>3</sup> Therefore, they must have been destroyed by the poison or have undergone natural death with no regeneration. But 75 per cent of the white cells would not die naturally in three days, and the degenerated forms of leukocytes, both mononuclear and polymorphonuclear, found in the circulating blood argue for poison. The polymorphonuclears suffer most, in correspondence with the severer injury in the marrow as compared with that in the lymphadenoid tissues, just the reverse of what occurs in exposure to roentgen rays. The red blood cells are less affected, no more than can be accounted for by natural death of cells. The increase of the

3. See, however, Pappenheim and also LeNoir and Claude, p. 19.

pigment content of the spleen is not great and may be accounted for, in part at least, by the destruction of nucleated red blood cells in the marrow. Selling quoted Heinecke as observing the same thing, in experiments with roentgen rays. In both his and Heinecke's experiments there were only slight changes in the red blood cells, in spite of the advanced degree of aplasia of the marrow. The red blood cells return to normal more slowly, yet in the early stages of the regeneration of the marrow the erythroblasts are often very much more abundant than the granulocytes.

Selling emphasized the stimulating effect of benzene on the marrow cells: Stimulation and destruction are constantly associated, the former prevailing at first, the parenchymal cells increasing rapidly, especially the more highly differentiated cell types. But this hyperplastic marrow begins to show well marked destruction of cells by the end of the second day, and the destruction increases, leaving empty spaces with edematous reticulum and wide capillaries, till only isolated cells are left, and after about the ninth injection the marrow is almost wholly aplastic. Erythroblasts, granulocytes and megakaryocytes are all affected, but in the polymorphonuclear amphophils the proportion of degenerated cells is always least. They disappear rapidly, however—probably being swept into the circulation. Small lymphocytes and polyblasts are found in considerable numbers and have the greatest resistance, persisting and apparently increasing after all others have been destroyed.

Selling's "ascending" series comprised those animals in which regeneration took place after aplasia of the marrow. In the early stages of regeneration, islands of cells appear in the reticulum, erythroblasts chiefly or granulocytes or large lymphocytes, which are abundant, and between these islands lie small lymphocytes and polyblasts. Other collections of cells form cords in radiating bands. Megakaryocytes are present, scattered or in bands. As regeneration progresses, the younger cells—the large lymphocytes, myeloblasts and megaloblasts—form an ever diminishing proportion. Regeneration can occur after an advanced degree of aplasia. Selling believed that the small lymphocytes and polyblasts play the chief rôle in the regenerative process, the steps being from small lymphocyte to large lymphocyte and then to megakaryocyte.

The lymphocytes in the follicles and medullary cords of the lymph glands show degenerative changes, following injections of benzene, within twenty-four hours, increasing as the experiment goes on. Large phagocytic cells pick up part of the debris of these cells. The follicles are progressively emptied, and the sinuses dilate, but aplasia is never complete: the changes are less marked than in the marrow. Regeneration is complete in from ten to fifteen days, but there may be some

fibrosis resulting from the irritating action of benzene. The changes in the spleen are similar to those in the lymph glands, but during regeneration, especially during the later stages, myeloid metaplasia occurs, with myeloid cells of all types. These are, however, relatively few in number, and at this stage the marrow is hyperplastic. Therefore, the myeloid metaplasia of the spleen can have little significance as a compensatory phenomenon.

Selling stated positively that benzol is a leukotoxic poison, destroying not only the tissues that produce leukocytes, but also the leukocytes in the circulating blood, since their decrease comes on too rapidly to be accounted for by natural death or by the injury done to the tissues.<sup>4</sup>

A well known byproduct of the publication of Selling's studies was the deliberate utilization of the leukotoxic action of benzene to reduce the white cell count in leukemic patients. The results obtained in these experiments on human beings are discussed in another section, but a secondary effect was the stimulation of interest in the physiologic action of benzene and a sudden outburst of articles on benzene poisoning in animals. Many of these were confirmatory of Selling's work, but some new details were added. Thus Secchi administered benzene by inhalation, injection and ingestion, and produced not only an enormous diminution of leukocytes, but a fall of hemoglobin to 50 per cent or less, a loss of red cells, a fall in specific gravity, a low color index, and poikilocytosis and stippling. The viscosity of the blood was increased when the benzene was administered in vapor form. At autopsy Secchi found that acute poisoning caused intense congestion of all the organs, and that chronic poisoning caused fatty degeneration and numerous hemorrhages, subpleural and into the mucosa of the intestinal tract and the genital tract.

Brandino's experiments are interesting, and since they are not available to most English-speaking students, I will venture to give them in detail.

He studied the lymph glands, marrows and spleens of dogs and rabbits to which benzene had been administered by inhalation, by ingestion and subcutaneously. In the lymph glands there is a notable destruction of the lymphocytes, which show karyolysis and karyorrhexis and fragmentation of chromatin. The débris is taken up at first by phagocytes; then these cells disappear; there is retraction of the reticulum and flattening of the follicular region, while the peripheral and medullary canals dilate. The medullary tracts are much less affected than the

---

4. Ronchetti also said that leukopenia comes on quickly, before the leukopoietic organs could have undergone marked involution. Therefore, one must add to atrophy of these organs intensification of the destructive processes in the circulating blood.

follicles, which are finally reduced practically to the reticulum. If the benzene is stopped, however, there is complete regeneration. Similar changes take place in the spleen, but here also there may be complete regeneration, during which myeloid metaplasia occurs. At the same stages there is less degeneration of cells in the spleen than in the lymph glands, and it is not so marked in the malpighian corpuscles as in the stroma. In the former the cells disappear first at the periphery, leaving a compact mass of cells at the center which, with the progress of poisoning, diminishes gradually till all the lymphocytes are gone and the malpighian body is recognized only by the disposition of the reticulum and the central vessel.

Brandino also found that benzene acts as a stimulus to the marrow, as well as a destroyer. At first the former action predominates, causing a rapid and notable increase especially of the most highly differentiated blood cells, while the myelocytes and megaloblasts are less affected. After the third or fourth injection hyperplasia begins to yield to destruction, till only narrow cords of cells are left, with edematous reticulum and dilated capillaries between. Then regeneration begins, which progresses rapidly and goes on to hyperplasia. The most resistant elements are the small lymphocytes and the polyblasts, which are found in the marrow after all others are gone. The spleen in advanced stages shows myeloid cells of all types.

Orzechowski (1929) noted that all experimenters had agreed that the red blood cells are not affected in chronic benzene poisoning, which is hard to understand, since more recent work was shown that the red corpuscles and the leukocytes have a common mesenchymal origin.<sup>5</sup> He employed Selling's technic, using rabbits, and in sixteen experiments found no change in the red cell count or in the character of the cells. Stippling was seen in one animal only; the loss of hemoglobin (Sahli) was slight; staining was normal. Therefore he held it to be evident that benzene does not attack the tissue which forms red blood cells. The histiogenic leukocytes (monocytes) were injured, but nothing like so much as the granular polymorphonuclears. The platelets were normal, and the clotting time in the warm chamber was normal in most cases. The leukocytes fell from 13,900 on the first day to 1,300 on the seventh and to 400 on the eighth day, following the last dose.

---

5. It is not, however, strictly true that all students of experimental benzene poisoning found an absence of attack on the red blood cells. Not only Secchi (see a foregoing paragraph), but Fontana, found a lowered red cell count and a loss of hemoglobin in animals, although this was not so striking as the loss of white cells. Mauro found anemia with poikilocytosis and anisocytosis in the late stages, and Duke, in seeking to produce a loss of platelets, produced also severe anemia, with benzene. In Weiskotten's experiments with inhalation of benzene, loss of red cells was observed (see page 31).

Orzechowski concluded that the severity of the attack of benzene is on the granulocytes, and he pointed out that this corresponds with what occurs in the central nervous system, where it is a rule that the latest cells in phylogenic and ontogenic development are the most vulnerable to all injuries.

Wallbach endeavored to distinguish the action of benzene in producing leukopenia from that of thorium X and that of x-rays, soft and hard. Benzene has a destructive action on the spleen and lymph nodes and also inhibits the formation of new cells by the bone marrow and the further differentiation of immature cells, so that there is a delivery to the circulating blood of granulocytes, polymorphonuclear with a swing to the left (Arneth). Thorium X causes a release of leukocytes into the blood stream and an inhibition of the formation of new cells but not of differentiation of immature cells; therefore the leukocytosis in this case is of mature cells. Soft x-rays do not diminish the white cell count, but there is a conspicuous increase of eosinophils and of mast cells, while hard rays injure the lymphatic tissue, although a marked leukopenia is never produced. The increase of eosinophils and of basophils is not as great with hard rays as with soft.

Pappenheim and Neumann both challenged some of the observations of Selling. Thus Pappenheim believed that the decrease of leukocytes is not so great as examination of the peripheral blood suggests, for he found in rabbits that at a stage when the white cells had almost disappeared from the circulating blood they were found in some cases still very abundant in dilated capillaries of the liver, lungs, spleen and kidneys.<sup>6</sup>

Neumann was unable to find fatty degeneration, as Selling found, but always found a striking hyperemia of the spleen, not mentioned by Selling. The spleen showed aplasia, but also pigmentation. The bone marrow was hypoplastic, as described by Selling, but Neumann never found the numerous small lymphocytes and polyblasts described by Selling, and found much more pigment. Some animals had pigment in the spleen, others in the liver and marrow, and the quantity was enormous in comparison with the controls. This could not be the result of chance, but hardly the result of blood destruction either, because of the slight loss of red blood cells, especially in that animal which had the largest amount of pigment.

Neumann emphasized the great variations in individual animals in their reaction to benzene, which explains the varying results in patients treated with benzene. For example, two rabbits were given the same

6. The only other observers to note an accumulation of leukocytes in the internal (intestinal) capillaries were LeNoir and Claude in a man dying of chronic benzene poisoning.

dose; the second lived seven days longer than the first. A third animal had a larger dose, but lived longer than the first. A fourth had the smallest dose and died the most promptly.

The organic lesions noted in animals are, on the whole, more marked and extensive than those found in most of the autopsies on human beings (see page 64). Chassevent and Garnier found in guinea-pigs congestion of the peritoneum and of the abdominal organs and not only ecchymoses, but ulcerations, in the gastric mucosa at the niveau along the artery. Klemperer and Hirschfeld found more or less severe destruction of marrow and extensive necrosis of liver and kidneys. Pappenheim also noted necrosis of the liver in rabbits and severe injury to the parenchyma of the kidneys.

Mention must be made also of some observations with regard to the action of benzene made by certain investigators in the course of their work on general problems. Underhill and Harris, working on creatine metabolism, tested the effect of injections of benzene with oil in rabbits and found that benzene not only acts on the blood elements, but that it exerts a catabolic influence on the body tissues as a whole, as manifested by a sharp rise in the excretion of creatine and total nitrogen within a very short period after subcutaneous injection, far in excess of that found in rabbits under ordinary starvation.

Jaffé examined the excretion of benzene in rabbits and dogs, giving them a daily dose of from 2 to 3 Gm. by mouth. He found that it was excreted in the urine partly as muconic acid by oxidation of the ring,  $C_6H_6$  plus  $O_2$ . Following him Fuchs and Soos isolated muconic acid from the urine of a leukemic patient who under Koranyi's treatment was being given benzene. He excreted from 3 to 5 Gm. of muconic acid in twenty-four hours. These authors believed that the production of muconic acid as an intermediate stage may be assumed to take place, but its detection is prevented because of the ease with which it forms combinations and changes to other bodies, such as acetone.

The prolonged bleeding time and clotting time in human benzene poisoning and the failure of the clot to contract led students of the physiology of the blood to study this feature of its toxicology. Duke found in rabbits a rapid rise in the platelet count, followed by a rapid fall. Severe anemia went with this, and at autopsy the marrow was found to be almost completely aplastic; megakaryocytes were hardly to be found. In large doses, 5 cc., benzene acted first as a stimulant, then as a poison to the platelet-forming organs, causing first a rise, then a fall in the count. In small doses, 2 cc., it acted only as a stimulant, causing a gradual rise in platelet count, which later fell, but not below the normal. In every instance, human and experimental, in which the platelet count fell to a low level (61,000 was the lowest) purpura

hemorrhagica was observed. The reason for the rapidity of the rise and fall in the number of platelets is to be found in the short life of the platelet.

Hurwitz and Drinker studied "the factors of coagulation in the experimental aplastic anemia of benzene poisoning." In addition to their observations with regard to the clot-forming substances in the blood, their work brings out clearly the contrast between clinical and experimental benzene poisoning already pointed out by Selling and others. Benzene has an important influence in reducing the circulating prothrombin, but antithrombin and fibrinogen fluctuate little from the normal, results which are in harmony with proofs recently discovered that blood platelets contain prothrombin. The latter originates from the megakaryocytes of the marrow, but other tissues also play a part in its formation. Any toxin which diminishes the number of platelets diminishes the available prothrombin in the circulating blood. In most instances in which the circulating prothrombin is diminished, aplasia of the bone marrow occurs. The appearance of an extreme aplasia without fatal diminution of prothrombin suggests (1) that other tissues or organs are concerned in its formation, or (2) that a minimum amount of myeloid tissue is sufficient to maintain the quantity of prothrombin above a dangerously low level.

These writers used rabbits and followed Selling's technic. Benzene was shown to be a myeloid tissue poison. Their experimental animals did not show marked hemorrhagic features and did not as a rule show prolonged bleeding time or bleeding from the gums and mucous membranes, etc. In a few instances at autopsy the blood remained fluid a long time. In spite of the absence of hemorrhage, striking changes were found in the blood, in the formed elements and in the prothrombin, though not sufficient to cause a clinical picture of hemorrhagic disease. They confirmed the observations of Selling and of Duke, viz.: a rapid disappearance of the white cells from the peripheral circulation, sometimes after an initial rise; red blood cells much less affected, sometimes not at all, in most cases reduced by 50 per cent; platelets showing the same general reduction, but to a less extent, remaining at a high level after the white cells have almost disappeared from the circulation. In only one animal were the platelets low enough to produce symptoms of a hemorrhagic disease.

Selling thought that the polymorphonuclear amphophils in the marrow are more resistant than the large lymphocytes, myelocytes, erythroblasts and giant cells. Hurwitz and Drinker suggested that either the megakaryocytes of the marrow regenerate very rapidly or they are more resistant to the action of benzene than are the forerunners of the polymorphonuclear leukocytes and erythrocytes.

The effect of benzene on the formation of antigen was tested in 1914 by Rusk in California and by Schiff working in Heffter's laboratory in Berlin. Rusk injected 1 cc. of benzene per kilogram of body weight into rabbits either before or at the time of the injection of antigen and found a decided reduction in the formation of lysin for sheep's corpuscles and of precipitin. Schiff gave guinea-pigs intraperitoneal injections of 0.01 cc. of benzene before an injection of antigen and found that there followed only slight leukocytosis and increased sensitivity to a second dose of antigen, while if he gave 0.03 cc., leukopenia developed, and sensitivity was diminished.

Simonds and Jones studied the curve of the production of antibodies in animals exposed to the x-rays, which exert a destructive effect, especially on the lymphadenoid tissue, and in animals treated with benzene, which exerts its chief effect on the bone marrow. For antigen they used washed dog's corpuscles and killed typhoid bacilli, and studied the degree of hemolysis and of agglutination. There was a high death rate in the animals treated with benzene, for they succumbed readily to spontaneous infections, and when the white cell count fell to 1,000 or less, they died even without evidence of infection. Benzene was given in doses of 1 cc. per kilogram of body weight in 2 cc. of olive oil, subcutaneously.

They found that while the most pronounced destructive effect of benzene is on the polymorphonuclear leukocytes, the lymphocytes are also affected. The power to produce hemolysins for dog's blood is much reduced by benzene, as is also the production of agglutinins and opsonins, in that order. They reasoned that the part of the blood-making system which has to do with the production of erythrocytes may be a factor of some importance in the formation of hemolysins, for the curve of the latter was similar in two rabbits with leukopenia and in the one with leukocytosis, but in all three animals the erythrocytogenic power was affected—as shown by the absence of nucleated red cells and stippled cells. The agglutinating power of the blood for killed typhoid bacilli was only from one half to one tenth of the normal, and the loss was greater in the animals treated by injection of benzene than in those exposed to the x-rays and was not in proportion to the leukocyte count. Opsonins were diminished by benzene but not so much so as agglutinins.

The fact that benzene had shown a selective action on tissues and cells that are concerned in the defense of the body against infection led Hektoen to test its action on the production of antibodies and on the activity of leukocytes. He used benzene and olive oil in equal parts for hypodermic injection into rabbits which had had, or were to receive, 30 cc. of sheep's blood in the peritoneal cavity. A quantitative determination was then made of the newly formed lysin and precipitin. Hektoen confirmed the results of Selling and others as to leukopenia,

especially of the granular leukocytes, preceded sometimes by a leukocytosis of moderate degree after the first injection. There was also in a number of animals a second increase in the leukocyte count, followed by a secondary fall before a return to the normal figure (see Weiskotten). The death rate was high in animals with profound leukopenia, and the marrow was found to be poor in cells. The loss of red cells was not great.

The production of specific precipitin and lysin was greatly reduced, but the course of antigen in the blood appeared the same in benzenized animals as in controls. At the height of the production of antibodies the injection of benzene appeared to have but little effect on the leukocytes of the blood and on its antibody content. That benzene acts on the elements that elaborate antibodies and that leukocytogenic centers are concerned in this elaboration was indicated not only by the reduction of antibodies and of leukocytes in the rabbits, but also by resistance to this effect when the production of antibodies was at or near its height, and by the leukocytosis and increased formation of lysin in dogs under the influence of small doses. Just how benzene interferes with the elaboration of antibodies, whether by direct injury to the cells or possibly by modification of enzyme action, is still a question. The action of benzene does not show that certain specific elements are concerned in the elaboration of antibodies because its action is too general, affecting, it is true, the granular leukocytogenic centers most, but the lymphocytes and the erythroblasts, as well. Hektoen concluded that benzene may lower the anti-infection powers of the body in at least three ways: by reduction of antibodies, by reduction of the number of leukocytes and by reduction of the phagocytic action of the leukocytes.

These conclusions were confirmed by experiments on the course of infection in benzenized animals. Thus Winternitz and Hirschfelder, while working on pneumonia, tested the effect of injections of benzene on the resistance of animals to pneumococci. They first reduced the white blood cells by means of benzene and then produced pneumonia by intratracheal inoculation with cultures of virulent pneumococci, and they found a marked reduction of resistance to the infection. The average duration of life after inoculation of the control animals was sixty-one hours, while in the animals treated by injection of benzene it was only twenty hours. The leukocytes were reduced in six rabbits to from 280 to 880. There was no difference in the gross appearance of the lungs in the two groups, but microscopic examination of the pneumonic exudate showed, in the benzenized rabbits, only occasionally a polymorphonuclear leukocyte or undifferentiated mononuclear cell, although the exudate contained the usual number of red blood cells and fibrin.

White and Gammon, inoculating rabbits with tubercle bacilli and administering benzene by inhalation, found that the latter lowered the resistance of these animals as compared with controls, but were unable to find the explanation of this result.

Camp and Baumgartner studied the effect of benzene on the course of inflammatory processes produced by chemical irritants, by heat and by the injection of unsterilized foreign bodies. They used Selling's method, injecting 2 cc. per kilogram daily till the leukocyte count fell below 1,000, then smaller doses. If they gave smaller doses from the first, there was a marked loss of weight, but without pronounced leukopenia. The best results were obtained by two or three doses of 2 cc., then from two to five doses of 3 cc. till leukopenia appeared, then doses just large enough to keep the white count low. Inflammation was produced by (1) croton oil rubbed into a deep scratch on the ear; (2) intramuscular injection of an aqueous solution of carmine and (3) immersion of the ear for three minutes in water at 55 C. Non-benzenized animals were, of course, used as controls.

They did not find the initial rise in the white cell count described by Selling, but if one dose of the series was omitted, a rise would occur. Croton oil normally causes a marked inflammatory reaction in from twenty-four to forty-eight hours, edema, and dense infiltration of the tissues with polymorphonuclear leukocytes. In the animals treated with benzene no gross changes were found, except in one, in which there was pronounced edema. In this same animal microscopic examination of the area showed a few lymphocytes; in the others, no leukocytes were to be seen. Masses of bacteria were found, evidently multiplying rapidly in the tissues and meeting little or no resistance. The most essential histologic difference between the benzenized animals and the controls was the absence of leukocytes in the inflamed areas.

Heat of 55 C. caused in the control animals rapid swelling and congestion of the ear; under the microscope edema, congestion and a considerable number of leukocytes were seen, but the latter were much less numerous than in the first series. In the leukopenic animals there were immediate swelling and congestion, but no collection of leukocytes. In the series treated by injection of carmine, microscopic examination of the controls showed that the particles of carmine soon became surrounded with polymorphonuclear leukocytes, which ingested the particles, and that then by the end of the second day a proliferation of connective tissue began. In the leukopenic animals, only two had any leukocytes around the masses of carmine and one of them had a terminal rise in the white cell count to 3,800, the other to 1,000. There was no proliferation of connective tissue in any. The carmine was not sterilized; none of the controls showed any bacteria in the tissues, while almost

every one of the leukopenic animals showed masses of bacteria in the collections of carmine and in the surrounding tissues.

These experiments showed that in almost every instance there is no leukocytic exudate in rabbits which have a severe leukopenia, and that there is an absence of antibacterial bodies "which may not be due entirely to the destruction of the leukocytes, since benzene probably has a generally cytotoxic, as well as a leukotoxic, action." Benzene was given to one of the rabbits with severe leukopenia which had developed a large abscess in the neck. It died when the white cell count fell to 600, but there was no effect on the abscess and benzene did not destroy the leukocytes in the abscess. Congestion of the blood vessels and edema occurred independently of the leukocytes. When the leukocytes were below 1,000, croton oil and heat produced no leukocytic exudate in the tissues of the ears, and carmine none in the muscles.

Weiskotten and his colleagues published, between 1915 and 1923, a series of studies covering many aspects of benzene poisoning, their special interest being in the therapeutic use of benzene as a leukotoxic agent. In the first article (1915) they told of testing the compensatory function of the spleen in regenerating erythrocytes and leukocytes by giving benzene to normal and to splenectomized rabbits. They found in both the usual rapid decrease in leukocytes, with a primary rise in the count, followed by a secondary fall and a secondary rise to a permanent level. The polymorphonuclear leukocytes were chiefly affected. With the primary fall went a moderate, but definite, fall in erythrocytes, but after this the erythrocyte curve appeared to progress independently of the leukocytes, and in most animals was unchanged during the second fall in the leukocyte count. There was no essential difference in the blood curves of animals the spleens of which had been removed and of those with spleens intact, showing that in rabbits the spleen has no essential function in the destruction of leukocytes and erythrocytes, nor in their subsequent regeneration. The myeloid metaplasia of Selling is of no great importance as a compensatory phenomenon.

The second article (1916) deals in detail with the "diphasic" leukopenia. "In all cases where animals survived the primary fall in the leukocyte curve there followed a primary rise which in all instances reached a normal level, and in many the original level. (This is the 'protophase'). This primary rise was in each instance, independently of any further injection, followed by a secondary fall and then a rise to a normal level. In the secondary fall ('deuterophase') the leukocytic curve in almost all instances reached a level nearly as low as that reached in the primary fall, and in some instances even lower." "The deuterophase of the diphasic leukopenia was not accompanied by any

changes in temperature curve except in one animal which had very low counts at the primary and secondary falls, in which the temperature rose at the climax of both falls."

The mortality was practically as great during the second fall as during the first. In all animals surviving the second fall the leukocyte curve returned to the normal level and there was no further fall. Between the first injection and the onset of the deuterophase there was a period of from eight to eighteen days corresponding closely to the period required for sensitization after the injection of an antigen and suggesting that the deuterophase might be the result of an antigen-antibody reaction, but no changes in the temperature occurred and there was no difference between the protophase and the deuterophase.

The third article, by Brewer and Weiskotten (1916), treats of the urine in benzenized animals. During the first twenty-four hours after the first injection the total of the phenols of the urine increases and still more after the second injection. This increase persists forty-eight hours after the last injection; then there is an abrupt return to normal.

In Weiskotten's fourth article (1917-1918) spontaneous infection occurring in benzenized animals was studied with special reference to its effect on the diphasic leukopenia. In four rabbits the leukopenia did not appear, and it was found that during the daily subcutaneous injections, acute infection had developed, and in two of these animals it seemed that it might even have been present before the experiment and to have been "lighted up" after the injections began. In none of these did diphasic leukopenia occur, and in only one, aplasia of the marrow. The percentage of polymorphonuclears in these animals, instead of falling, rose in all to from 83 to 97 per cent before death. In three animals there was also leukocytosis.

The fifth article (1919) describes the diphasic leukopenia as being accompanied by a relative increase in polymorphonuclear amphophils. The small mononuclear cells are absolutely decreased at the climax of the first phase to a greater extent than are the polymorphonuclear amphophils. At the end of the second phase the total leukocyte curve reaches a level somewhat lower than that existing before the injections began, and this is due to the failure of the mononuclears to rise to as high a level as before injection. This is the only observation of its kind in the literature.<sup>7</sup>

Weiskotten's experiments to this point were made with injections of benzene. Experiments with inhalation (1920) were then made on

---

7. The reverse was found by practically all experimenters, with the exception of Fontana, who stated that although the lymphocytes survive longest in most cases, those that develop very rapidly may not show this inversion of the leukocytic formula.

11 rabbits, which died on various days from the first to the sixty-ninth. One of them lived till the fifth day after the experiment had ceased; another, till the sixteenth. The results were somewhat different from those obtained in the earlier series. The fall in the white cell count was as sharp, but never went as low as 1,000, even if the experiment continued 53 days. Attempts to bring about a more marked leukopenia by higher concentration of benzene were fatal to the animals. After the experiment ceased, the low count persisted for from 12 to 36 days, then gradually, in from 36 to 51 days, rose to a permanent level, which was considerably lower than that existing before the experiment began, and which was maintained as long as the counts were made, in no instance returning to the normal level even after from 368 to 458 days. The average count for three animals was 11,302 before, and 6,166 after, the experiment. There was no deuterophase, as after injections. The red cells fell to a low level in from 6 to 16 days, and stayed there as long as the experiment continued, but with no tendency to fall lower, and after the experiment ceased they rose to the former level in from 15 to 24 days. The average fall was from 6,126,000 to 4,947,000.

In his last article, published in 1923, Weiskotten stated that the diphasic leukopenia is a direct result of the necrosis of bone marrow produced by benzene, and that the final return of the leukocytes to a normal level is due to active regeneration of the leukoblastic elements of the marrow. The erythroblastic elements of the marrow also undergo necrosis and regeneration, but the circulating red corpuscles are apparently little affected, and their curve shows slight changes, if any, following injections of benzene. There is a temporary increase of thrombocytes in the circulating blood at the beginning of the experiment, and as the resulting necrosis of the bone marrow gradually progresses, there is a progressive decrease in thrombocytes which lasts during the entire period of necrosis. Active regeneration of the bone marrow is accompanied by a marked increase in the number of thrombocytes, which passes the normal limit and then falls to normal, thus furnishing additional evidence of the formation of thrombocytes in the bone marrow. The histologic examination of the marrow of animals dying or killed at times coincident with the beginning of thrombocytosis shows large numbers of megakaryocytes in the regenerating marrow.

#### EXPERIMENTAL POISONING IN MAN

The action of benzene has been studied by a number of observers in connection with its therapeutic use in the treatment for various forms of leukemia. Its use was first advocated by Koranyi in 1912, and he gave it greater publicity at the International Congress of Medicine in

London in 1913, when he reported on the results in eighty cases, not all of which were his own. He noted that high doses may destroy the red blood cells, whereas the proper dose stimulates their production up to a count of 6,000,000. An overdose or too prolonged treatment may cause hemorrhages in the skin and mucous membranes, anemia of a high grade, fever and almost complete disappearance of leukocytes; i. e., a typical picture of aplastic anemia or thrombopenic purpura, which is always fatal. Another danger is the continuance of the effect of benzene after the dose is stopped.

Billings, in 1913, reported favorably on this form of treatment in five cases, but also warned against possible bad results. He found that there was a tendency first to a rise in the leukocyte count, followed in from ten to fourteen days by a rapid fall and by a diminution in the size of the spleen and liver, more rapid than with treatment by the x-rays alone. Usually at this stage there was also an increase in the red cell count and in the hemoglobin, but the effect was not so marked as on the leukocytes. The effect was more rapid in lymphoid, than in myelogenous leukemia, with a rapid fall in the white blood cells, which were seen in blood smears to undergo early and marked degeneration. Spiegler, in 1914, administered benzene for three weeks to a woman with myeloid leukemia, with decided success. She went home and without authorization kept on with the benzene for five weeks more (the quantity is not given). She returned to the hospital very anemic, with a count of 2,600,000 red cells; the white cells, which at the outset had numbered 150,000, were now only 1,400, almost all of them lymphocytes, none myelocytes. This change came without any diminution in the size of the spleen. Three months later she had bleeding from the gums and suffusion of blood under the skin. The cell count was about the same, but the blood did not clot. At one count the leukocytes numbered only 400. The axillary temperature was from 37 to 39 C. (98.6 to 102.2 F.). Toward the end, ulcers appeared on the epiglottis, and ten days before death the first hemorrhage occurred. The granular leukocytes practically disappeared. This change could not be spontaneous, for myeloid leukemia never changes to leukopenia. It must have been the result of the action of benzene, which injures myeloid, far more than lymphadenoid, tissue. Spiegler quoted Klein on a case, also of myeloid leukemia, in which the leukocytes sank from 988,000 to 1,720 under benzene therapy.

Other cases described in the literature are those of Schmidt, Kiralyfi and Neumann. The last named described the case of a man who, after improving under the treatment with benzene, with diminution of the leukemic tumors and a fall in the white count from 56,000 to 5,300, suddenly grew worse; fever, hemorrhage and leukopenia developed,

followed by death. The marrow was aplastic just like that in the experimental benzene poisoning of Selling.

Ronchetti and Stein found in leukemic patients treated with benzene a disappearance of the nucleated red blood cells from the circulating blood, even when there was no intolerance of the cure. Ronchetti said that Fontana found that basophil red cells disappeared. The fall in the white cells in benzene therapy affects first the immature forms, and its action is quicker and intenser in leukemic persons with many immature white cells than in nonleukemic persons, as shown in the experiment of Vaquez and Jacoul, who tested it in a normal man and in a patient with myeloid leukemia. In the former the white cells fell from 7,800 to 3,000; in the latter, from 800,000 to 16,000. Ronchetti himself administered benzene to a woman with Hodgkin's disease, who recovered when all else had failed. In three weeks the white cells had fallen from 8,906 to 260. The patient had chills and fever, nosebleed and disappearance of platelets; but this was followed by a rise of the white cell count to 5,312, a reappearance of platelets and recovery from the benzene poisoning. According to Ronchetti, this shows the action of benzene to be toxic to the circulating leukocytes and platelets rather than causing atrophy of organs, or the recovery would not have been possible.

*(To be Continued)*

## Notes and News

---

**Popular Science Monthly Award for Achievement in Science.**—The first annual award of \$10,000 "for the current achievement in science of the greatest benefit to the public" has been divided between George H. Whipple, professor of pathology in the University of Rochester, and George R. Minot, professor of medicine in the Harvard Medical School, in recognition of work on the influence of the liver on blood regeneration and of the application of liver extracts to the treatment of pernicious anemia.

**University News, Promotions, Registrations and Appointments, etc.**—Hugh E. Burke has been appointed director of the research laboratory at the New York State Tuberculosis Sanatorium, Ray Brook, succeeding David T. Smith who resigned to become associate professor of medicine at Duke University.

Charles Krumurede, assistant director of the research laboratory of the Health Department of New York City and professor of hygiene and bacteriology in New York University, has died at the age of 51 years.

The William Wood Gerhard Gold Medal of the Philadelphia Pathological Society was presented on Jan. 8, 1931, to Simon Flexner, director of the Rockefeller Institute for Medical Research.

In the Indiana University School of Medicine, W. A. Brumfield has been appointed instructor in the department of bacteriology and pathology and Wemple Dodds promoted from instructor to assistant professor.

According to the *British Medical Journal*, the Nordhoff-Jung Cancer Prize for the best recent work on cancer has been awarded to Alexis Carrel, of the Rockefeller Institute for Medical Research, for his methods of tissue culture and its application to the problems of growth of tumors.

David Marine has received the gold medal of the New York Academy of Medicine for his investigations of the thyroid gland.

J. H. Teacher, St. Mungo (Notman) professor of pathology in Glasgow University, has died at the age of 61 years.

Major G. Seelig is directing the cancer program of the Barnard Free Skin and Cancer Hospital in St. Louis.

**Undulant Fever.**—It is reported that the French Government has accepted an offer by the Rockefeller Foundation to establish a center for the study of undulant fever at Montpellier.

**Bacterial Nomenclature.**—The International Society for Microbiology has taken up bacterial nomenclature as part of its permanent program. The matter has been placed in charge of a committee, of which R. S. Breed, New York Agricultural Experiment Station, Geneva, is one of the secretaries. The year of the publication of Linnaeus' *Species Plantarum*, namely, 1753, has been adopted as the date of departure for eventual international agreements in the naming of bacteria.

**In Honor of James Ewing.**—The homage volume issued to commemorate his sixty-fourth birthday, was presented formally to James Ewing at a large dinner in his honor on Jan. 31, 1931.

## Obituary

---

VERANUS ALVA MOORE

1859-1931

In the early morning of Feb. 11, 1931, death claimed Dr. Veranus A. Moore, who, prior to his retirement in 1929, for thirty-three years had been professor of comparative pathology and bacteriology in the New York State Veterinary College at Cornell University, and for twenty-one years had served as its dean and director.

Dean Moore's life was largely shaped by an accident which he suffered as a boy of 13 on his father's farm in Jefferson County, New York. He stepped on a nail, and an infection of the bone resulted which forced him to walk with crutches until he was 25 years old. Seeking aid for his affliction, the young man visited many physicians and hospitals and gradually became much interested in medicine. His disability was finally removed almost completely by an operation. After graduating from Cornell University with the B. S. degree in 1887, he pursued medical studies at Columbian University (now George Washington University) in Washington, D. C., and received his M.D. degree in 1890, while serving as an assistant in the pathological division of the Bureau of Animal Industry. In later years he received the degree V.M.D. from the University of Pennsylvania and that of D. Sc. from Syracuse University.

From 1890 to 1896, Doctor Moore was engaged in research in animal diseases with Dr. Theobald Smith in the Bureau of Animal Industry at Washington, some of his first scientific work being on Texas fever, which then was being actively investigated. He later collaborated on the researches on hog cholera, and worked independently on the disease of chickens, now known as fowl typhoid. He succeeded in isolating and proving the relationship of the causative organism to the disease. During the last year before his return to Cornell, Doctor Moore became the chief of the pathological division, succeeding Theobald Smith in this office when the latter went to Harvard.

Returning to his alma mater in 1896, Doctor Moore became a member of the original faculty of the New York State Veterinary College. He took an active interest in the infectious diseases of the domestic animals and soon became known as one well versed in his profession. On the retirement of James Law, in 1908, he was chosen director of the college.

Quiet and unassuming always, but nevertheless firm when firmness was demanded, Dean Moore proved to be an able and inspiring teacher, a capable executive, a true friend to his colleagues, students and other friends, a devoted worker for his University and the city in which he lived, and a wise counsellor to his state and nation in matters relating to the health of animals, and in the protection of the livestock as well as the human family from those diseases that are carried by animals.

Dean Moore engaged in many activities outside of his university work. He served his city on many occasions, especially on the school and health boards. When the federal meat inspection act was passed, he was a member of the commission which drew up regulations under which the law was to function. During the World War, he served in civilian capacity as an advisor on the organization of the Army Veterinary Service. In recent years, he has served as an advisor on the Milbank Foundation, and on President Hoover's White House Conference on Child Health.

Dean Moore was the author of many scientific articles dealing with animal pathology and especially with bovine tuberculosis, on which he was recognized as an authority. He was the author of several books, the best known of which are his "Pathology and Differential Diagnosis of the Infectious Diseases of Animals" and "Bovine Tuberculosis and Its Control."

W. A. HAGAN.

## Abstracts from Current Literature

### Experimental Pathology and Pathologic Physiology

HIGH ELECTRICAL RESISTANCE OF THE SKIN OF NEW-BORN INFANTS AND ITS SIGNIFICANCE. CURT P. RICHTER, *Am. J. Dis. Child.* **40**:18, 1930.

The resistance offered to the passage of a galvanic current through the body of a new-born infant is much greater than that in adults. The resistance of the skin on the backs of the hands (dorsal resistance), which is typical for the skin on the rest of the body, is very high. In some infants it is so high that the skin is almost completely impermeable. It was pointed out how this high dorsal resistance reflects a high degree of muscular relaxation in the infant. The resistance of the skin on the palms of the hands (palmar resistance) also is much higher than that which is found in adults. It was shown how the palmar resistance is correlated with the sleep of the infant; that is, the deeper the sleep the higher the palmar resistance. The general significance of these observations in the understanding of the physiology of the new-born infant was discussed. It was shown how the presence of an inhibition of the sympathetic and a possible dominance of the parasympathetic is indicated through the high palmar resistance in the new-born infant. It was pointed out that according to previous results the high dorsal and palmar resistance would indicate a very small amount of insensible perspiration and sweating in the new-born infant.

AUTHOR'S SUMMARY.

THE PROBLEM OF DENTAL CARIES. R. W. BUNTING and Others, *Am. J. Dis. Child.* **40**:536, 1930.

In the study of the cause and control of dental caries there is need for a fuller understanding of basic facts concerning the disease which have already been established. Many theories have been advanced that are not in accord with known facts. Evidence is given in support of the view that dental caries is a specific infective process, the activity of which is dependent on certain metabolic states. As the result of dietary and therapeutic experiments, active dental caries was reduced to a negligible quantity in 433 children. Of the methods employed, dietary measures appeared to be the most important. The diets prescribed for the control of dental caries were well balanced, well fortified, adequate rations in which sugar was reduced to the minimum.

AUTHORS' SUMMARY.

THE CORPUS LUTEUM AND THE MENSTRUAL CYCLE. CARL G. HARTMAN, *Am. J. Obst. & Gynec.* **19**:511, 1930.

Menstrual bleeding is held to be foreshadowed and typified in the lower animals, especially the primate. A study in the *rhesus* monkey shows that ovulation is not essential for menstruation, which occurs without any sign of recent ovulation. Hence the corpus luteum is not the underlying factor in producing the rhythmic menses. The corpus luteum, on the other hand, is inevitably associated with premenstrual hypertrophy. The association appears to be one of cause and effect, although Hartman is loathe to conclude this. He proposes that the causative factor of menstruation be sought outside of the ovary, though it cooperates with this organ in maintaining the menstrual rhythm. It is suggested that the hemorrhages of menstruation and implantation be considered as homologous processes.

A. J. KOBAC.

PLEURAL EFFUSIONS. MAX PINNER and GEORGINE MOERKE, *Am. Rev. Tuberc.* **22**:121, 1930.

Experiments on rabbits show that the normal pleura is highly permeable in either direction for the constituents of the blood. In patients with pleural effusions under pneumothorax treatment for pulmonary tuberculosis, a marked decrease of the pleural permeability is shown by actual experiments and must be assumed to exist from the results of chemical studies of the blood and the pleural effusion. Neither chemical, cytological, or serologic data afford, per se, dependable diagnostic or prognostic criteria. The failure of resorption of pleural effusion cannot be explained by the chemical constitution; it must be due to an alteration in pleural permeability.

H. J. CORPER.

ADDISON'S DISEASE IN A NEGRO: REPORT OF A CASE. ANGELO M. SALA and MENDEL JACOBI, *Arch. Int. Med.* **46**:375, 1930.

The fifth case of Addison's disease in a Negro, with autopsy observations, is recorded in detail. The other recorded cases are reviewed. A comparison is made with the disease in white persons. The difficulty of diagnosis and the prominence of symptoms not usually stressed in white people are emphasized. The laryngeal and respiratory symptoms are stressed particularly.

AUTHORS' SUMMARY.

THE REACTION OF THE CENTRAL NERVOUS SYSTEM TO EXPERIMENTAL UREA INTOXICATION. BERNARD J. ALPERS, *Arch. Neurol. & Psychiat.* **24**:492, 1930.

Alpers investigated the reaction of the interstitial tissues of the brain of the rabbit to intoxications with urea. Changes were present in both gray and white substances, but especially in the latter. The microglia showed no, or a very mild, reaction (thickening and hypertrophy of the processes); in a severe case, fusiform or nodular swellings were scattered over the processes. The neuroglia, mainly the fibrous glia, was profoundly altered, especially around the blood vessels. It appeared as swollen and hypertrophied cell bodies with formation, in one severe case, of ameboid glia and clasmatodendrosis. In the former the nucleus was shrunk and more or less pyknotic; the processes were greatly swollen; the cytoplasm became granular and finally homogeneous. The vascular feet were disintegrated; they became greatly swollen, vacuolated, at first coarsely and later finely granular and shrank considerably. Changes were also exhibited by the macroglia cells described by Andriezen, and termed perivascular neuroglia by Hortege, many of which became pulverized and were represented only by remnants of a coarsely granular cytoplasm. Oligodendroglia (glia nuclei) showed changes only in severe cases—the nucleus was swollen and vacuolated, and the cytoplasm reticulated and also swollen. In contrast, the ganglion cells showed mild changes (reduplication of the nucleolus). Fat granule bodies did not occur in this case. The fact that the neuroglia cells in close proximity to the blood vessels were especially affected suggests a possible function of the neuroglia "to neutralize the effect of noxious agents circulating in the nervous system, and in this way to protect the nobler elements against harm."

G. B. HASSIN.

EXPERIMENTAL LESIONS IN THE TUBER CINEREUM OF THE DOG. L. O. MORGAN and C. A. JOHNSON, *Arch. Neurol. & Psychiat.* **24**:696, 1930.

The authors succeeded in producing epileptiform seizures in dogs by injecting about 0.1 cc. of a weak solution (from 0.2 to 0.5 per cent) of mercuric chloride into the tuber cinereum. As in real epilepsy, the convulsions occurred periodically, the animals otherwise remaining normal. The convulsions, which began from two to six hours after the operation, were mild, in the form of dilatation of the pupils, salivation, muscular spasms of the face, the jaws and, to a varied extent, the anterior part of the body.

In a majority of cases the convulsions continued gradually to become severer and more frequent. The foregoing symptoms and signs were followed by rigidity, falling and general clonic convulsions of from one and a half to three minutes' duration. With the convulsive state over, the animal would remain unconscious for several minutes, then would be confused and disoriented. With the increase in frequency of the convulsions, the dog would pass into status epilepticus, and death was preceded by continuous coma, an increased rate of heart beats (from 230 to 260) and a rise of temperature (from 108 to 117 F.). The time from the beginning of the first convulsion to the death of the animal was usually from ten to twenty hours.

A chemical analysis of the blood in the animals experimented on showed: no changes in the calcium or potassium content of the serums, or any appreciable alteration in the potassium-calcium ratio. As the convulsions increased in frequency and severity, an inconstant increase of the nonprotein nitrogen and a decrease in the carbon dioxide combining power of the plasma resulted, while the sugar content of the blood first rose steadily to about twice the normal value and then sank steadily until the animal's death.

G. B. HASSIN.

THE PERMEABILITY OF THE HEMATO-ENCEPHALIC BARRIER AS DETERMINED BY THE BROMIDE METHOD. SAMUEL T. GORDY and STEPHEN M. SMITH, *Arch. Neurol. & Psychiat.* **24**:727, 1930.

In Gordy and Smith's studies of meningeal permeability, that is, the passing of chemical substances from the blood to the spinal fluid through the so-called hemato-encephalic barrier (the vascular endothelium in apposition with ependymal cells of the choroid plexus or with the meninges), they used the bromide method of Walter on 183 patients (108 men and 75 women). For deproteinization they utilized the nascent tungstic acid with the ordinary reagents used in the Folin-Wu system of analysis of the blood. The ordinary ratio between the bromide distribution in the blood and that in the spinal fluid—the permeability quotient—is about 3. This denotes that the concentration of bromide in the blood is three times stronger than that in the spinal fluid. In the majority of patients with dementia paralytica it was below 3, that is, it was increased. Some patients with schizophrenia showed a decreased permeability, about one half of them showed a normal permeability quotient, while some (24 per cent) showed an increased permeability. In the manic depressive patients about one half showed normal and the other half increased permeability. In cases of postencephalitis or senile psychosis, the conclusions were of no particular value; in patients with the alcoholic and arterio-sclerotic types of psychosis there was a marked tendency toward increased permeability. The authors also concluded that with the Walter bromide method it was not possible to differentiate between dementia praecox and the manic-depressive psychosis, and that the deviations of permeability quotients from the normal, occurring in patients with some form of psychosis, denote them to be organic lesions of the brain.

G. B. HASSIN.

PATHOGENESIS OF AMAUROTIC IDIOCY. CHARLES SCHAFER, *Arch. Neurol. & Psychiat.* **24**:765, 1930.

From a study of a few portions of the brain and cerebellum of a case of Niemann-Pick's disease, Schaffer concludes that in contrast to amaurotic family idiocy (Tay-Sachs' type), which is an endogenous ectodermal disease, the former is a disease of the mesodermal layer. Both are constitutional, congenital and familial diseases, characterized by racial predisposition. On account of their endogenous basis they may occur simultaneously, as a combined disease of the germ layer (of the ectoderm and mesoderm), but they are essentially different morbid entities. They also show some histologic differences. In Niemann-Pick's disease the cell expansion is far less pronounced than in Tay-Sachs' disease, and a fine prelipoid granulation is present only in the Purkinje cells, while in

Tay-Sachs' disease it is found in all of the cerebellar neurons; in Niemann-Pick's disease the fat-storing cells appear in the nerve parenchyma as prelipoid bodies, and a fine granulation with lipoid substances is present in the mesodermal tissues—the leptomeninges and the blood vessels. In Tay-Sachs' disease the fat-storing cells and the fine granulations are absent.

G. B. HASSIN.

EXPERIMENTAL FIBROUS OSTEODYSTROPHY (OSTITIS FIBROSA) IN HYPER-PARATHYROID DOGS. H. L. JAFFE and A. BODANSKY, *J. Exper. Med.* **52**: 669, 1930.

These experiments have shown that parathyroid extract (parathormone Collip) can be injected into puppies in increasing amounts for long periods without fatal results. Thus time is allowed for bone changes to develop. Long continued injection leads to progressive decalcification and resorption of the existing bone, to fibrous replacement of the marrow and to the production of the other features characteristic of ostitis fibrosa. Deformities eventually appear. It is safe to assume that the changes in the bone produced by hyperparathyroidization have the same pathogenesis as those observed in clinical cases believed to be instances of hyperparathyroidism—that is, cases with a negative mineral balance and decalcification of the skeleton.

AUTHORS' SUMMARY.

EFFECT OF SIZE OF EXPLANT ON CULTURES OF FIBROBLASTS. W. R. EARLE and J. W. THOMPSON, *Pub. Health Rep.* **45**:2672, 1930.

An attempt was made to study the influence of the size of the explant on cultures of fibroblasts of the chick, planted in a small, thin hanging drop of embryo juice and plasma. This medium was not changed during the life of the culture. The explants used varied from only a few cells to cell clumps about 1 mm. cube in volume. Fibroblasts from fresh chick heart and from a stock strain were used.

It was found that, for the cultures studied, the absolute increase in the area of a culture varied approximately directly as the size of the explant.

Further, the final maximal size of a culture also varied approximately directly as the size of the explant, and in cultures from the smallest explants it was very slight indeed.

MOTTLED ENAMEL IN A SEGREGATED POPULATION. G. A. KEMPF and F. S. MCKAY, *Pub. Health Rep.* **45**:2923, 1930.

At the present time no definite conclusions about the cause of mottled teeth can be drawn. From observations made over a period of years, the dystrophy of the enamel seems to occur in certain areas in the United States, and the etiologic factors seem to be definitely associated with the water supply. A child exposed during the period of growth of the permanent enamel to the environmental factors of an endemic area is almost certain to develop mottled enamel of the teeth. An excellent bibliography of reports on this disease covering the past thirty years is included at the end of this paper.

THE INTRAOCULAR PRESSURE AND DRAINAGE OF THE AQUEOUS HUMOUR. FREDERICK RIDLEY, *Brit. J. Exper. Path.* **11**:217, 1930.

The cornea is a normal and constant path of drainage of the aqueous humor. Drainage takes place chiefly via the filtration angle. The corneal path of drainage is probably the only one by which aqueous humor is normally and constantly removed. The sclera is not indistensible. Curves of distensibility are described, and their significance is discussed. The influence of expansion of the vascular

bed of the uvea on the intra-ocular pressure is demonstrated. A mechanism is described by which the intra-ocular pressure may be attained, maintained and varied. The manner in which failure of drainage may give rise to increased intra-ocular pressure is described. In a theoretical summary the conditions controlling the intra-ocular pressure and aqueous drainage are correlated, and their application to the problem of glaucoma is indicated.

AUTHOR'S SUMMARY.

THE PHARMACOLOGICAL ACTION OF THE EXOTOXIN OF STAPHYLOCOCCUS AUREUS. C. H. KELLAWAY, F. M. BURNET and F. ELEANOR WILLIAMS, *J. Path. & Bact.* **33**:889, 1930.

The intravenous injection of crude agar staphylococcal toxin into the cat and rabbit has a two-fold effect on the blood pressure. There is first a transient fall with recovery above normal, and secondly a rapid terminal fall. The initial transient fall is vasomotor in origin and is due to the presence in the toxin of pharmacologically active constituents of the media. After this initial fall the excessive rise during recovery is possibly contributed to by an increased output of epinephrine. In confirmation of the contention of Russ, the final fall in the blood pressure is shown to be due principally to obstruction of the pulmonary circulation. That there is a direct action on the heart which is contributory to the failure of the right side of the heart following obstruction is shown by the use of the isolated heart with an artificial pulmonary as well as an artificial systemic circulation. These phenomena attending the final fall of blood pressure do not occur in the immune animal, or in animals passively protected by antitoxin. The absence of complete protection by overneutralization with antitoxin is discussed, and the artificial nature of a test by intravenous injection is insisted on, since the toxin under these conditions reaches the heart and lungs in high concentration directly following the injection.

AUTHORS' SUMMARY.

ENCEPHALITIS PERIAXIALIS DIFFUSA IN A RHESUS MONKEY. J. R. PERDRAU, *J. Path. & Bact.* **33**:991, 1930.

The knowledge that Schilder's encephalitis occurs naturally in the rhesus monkey demands the exercise of great care that the natural disease is not mistaken for the experimental one when attempts are made to reproduce one of the human demyelinating diseases in this species of monkey. At the same time the rhesus is valuable as a susceptible animal for this particular type of encephalitis.

AUTHOR'S SUMMARY.

LIVER EXTRACT IN EXPERIMENTAL ANAEMIAS. G. PAYLING WRIGHT and BARBARA ARTHUR, *J. Path. & Bact.* **33**:1017, 1930.

The administration of an extract of liver, effective in the treatment of pernicious anemia, has no significant influence on the red cell or the reticulocyte counts of normal rabbits. The regeneration from anemia resulting from the injection of phenylhydrazine or from hemorrhage is not affected by the administration of the substance effective in pernicious anemia. Measurements of the diameters of the red cells together with the differences in the severity of the anemia indicate that the administration of liver extract mitigates the severity of the anemia produced by phenylhydrazine. This phenomenon is probably in no way concerned with the activity of the extract in the treatment of pernicious anemia. The administration of liver extract results in a diminution in the size of the polychromatic cells liberated from the marrow. It is suggested that liver extract acts in pernicious anemia by promoting the due degeneration of the megaloblastic phase of erythropoiesis.

AUTHORS' SUMMARY.

EXCRETION OF URINARY PIGMENT. LUDWIG HEILMEYER, *Ztschr. f. d. ges. exper. Med.* **72**:545, 1930.

The excretion of urinary pigment was determined in twelve cases of exophthalmic goiter. In three cases it was higher than normal. In each of these three cases there were signs of thyrotoxic circulatory failure. No association was noted between the amount of urinary pigment and increased metabolism. One case with a basal metabolism of +130 per cent showed no increase in urinary pigment as long as the circulation remained normal. Also, no change in the excretion of pigment was noted following therapeutic doses of thyroxine and thyroid gland. These observations tend to contradict the hypothesis of Dabkin, that a relationship exists between increased metabolism and the excretion of urinary pigment.

PEARL ZEEK.

VASONEUROTIC DIATHESIS. KARL A. BOCK, *Ztschr. f. d. ges. exper. Med.* **72**:561, 1930.

Investigations were made in regard to a group of diseases in which there were disturbances in the "vegetative-endocrine-electrolytic milieu." Certain cases of gastric and duodenal ulcer were included. In such cases long administration of thyroxine and of certain preparations of vitamins readily caused changes in form and function to appear in the capillary system, as viewed on photographic plates. Such changes did not appear in normal controls. In diseases associated with constitutional hypertension this reaction occurred very early in the disease, while the blood pressure was still relatively low and fluctuating. As blood pressure climbed higher and hypertension became permanent, the reaction disappeared. In persons of this diathesis the action of epinephrine was reduced, as compared with that in healthy persons, but after thyroid treatment it approached the normal. Also, in these persons, there was greater acidity of the tissues, but this factor may have been influenced by the diet. The increased acidity of the tissues might account for the type of reactions to epinephrine and thyroxine obtained in these persons, since the activity of these hormones is influenced by the degree of acidity of the tissues.

PEARL ZEEK.

ALTERATIONS IN LEUKOCYTES IN VITRO. HORATIO GOLDIE, *Ztschr. f. d. ges. exper. Med.* **72**:637, 1930.

Two groups of changes in leukocytes are described, necrobiosis and metamorphosis. The former is an expression of loss of vitality and disintegration of structure. The latter includes cellular hypertrophy, division and autolysis and represents acceleration of cellular processes. It may be brought about by various irritative factors.

PEARL ZEEK.

THE VITAL IMPREGNATION OF THE AORTIC WALL WITH TRYPAN BLUE. W. HACKEL, *Ztschr. f. d. ges. exper. Med.* **72**:762, 1930.

Experiments revealed that impregnation of the aortic wall with dyestuffs was more marked in animals with artificially increased blood pressure, than in those with normal blood pressure. The site of greatest infiltration seemed to be the same as that in which lipoidal degeneration is commonly found. The same applied to infiltration of the semilunar cusps of the aortic valve.

PEARL, ZEEK.

EXPERIMENTS ON THE PATHOGENESIS OF ASEPTIC AND ATRAUMATIC PLEURITIS. T. KANAI and K. MINAMI, *Ztschr. f. Tuberk.* **56**:434, 1930.

Exudative pleuritis occurs in about fourteen per thousand of all Japanese soldiers. It is very doubtful whether this pleuritis is tuberculous, since it is

much more frequent in the Japanese army than in Western armies, while the mortality from tuberculosis in Japan is essentially the same as that in Western countries. Experimentally it was shown that the intravenous injection of sympathicotonic drugs with forced bodily movements caused large pleural effusions. Parasympathicotonic drugs exert no such influences, and they even prevent the action of the former class of drugs. It is concluded that Japanese "military pleuritis" is caused by strictly metabolic and nervous disorders, due to the sudden change in living conditions.

MAX PINNER.

### Pathologic Anatomy

THE CORONARY ARTERIES OF THE DOG. ROBERT A. MOORE, *Am. Heart J.* 5: 743, 1930.

The coronary arteries of the dog differ from those of man in two major points: the presence of a distinct and separate septal artery as a branch of the left coronary artery, and the formation of the posterior descending artery by the left in all cases rather than in 20 per cent as in man. The origin and course of the septal artery render experimental ligation of it difficult. It is improbable that previous investigators have interrupted the blood supply to the septum. Anastomoses between the coronary arteries and their branches are extremely abundant in the dog's heart.

AUTHOR'S SUMMARY.

POLYPOID FIBROMA OF THE LEFT AURICLE (SO-CALLED CARDIAC MYXOMA) CAUSING A BALL-VALVE ACTION. G. H. HOUCK and G. A. BENNETT, *Am. Heart J.* 5:787, 1930.

A case of intracardiac tumor arising from the interauricular septum is reported and illustrated by gross and microscopic photographs. We have found no record of this condition ever having been diagnosed before necropsy. A tumor of this type may produce a ball-valve action in every way similar to the action of a ball thrombus.

AUTHORS' SUMMARY.

ANEURYSMS OF THE BRONCHIAL ARTERIES. MENDEL JACOBI, *Am. Heart J.* 5:795, 1930.

A case of multiple, saccular aneurysm of the bronchial arteries is reported, the first recorded in the literature. Death resulted from asphyxia caused by tracheal occlusion by the aneurysm. The etiology is shown definitely to be syphilitic, a rather unusual observation in aneurysms of smaller arteries. Many other small and several medium-sized arteries showed syphilitic involvement varying from the early lesions of endarteritis of the vasa vasorum and lymphocytic perivascular infiltration of the adventitia to extensive destruction of the elastic lamellae. The rôle of the supporting external structures in the formation of the aneurysms of the intercostal arteries and aorta in this case is indicated.

AUTHOR'S SUMMARY.

OSTEITIS FIBROSA CYSTICA: GENERALIZED TYPE WITH GIANT CELL SARCOMA. BENJAMIN M. JOSEPH, *Am. J. Dis. Child.* 40:81, 1930.

Microscopic sections of biopsy material showed giant cell sarcoma in an inguinal lymph node from a patient with generalized osteitis fibrosa cystica.

P. H. GUINAND.

CONGENITAL PNEUMOTHORAX. JACOB STEIN, *Am. J. Dis. Child.* **40**:89, 1930.

A case of congenital pneumothorax is described. A thorough review of the literature in all languages indexed at the New York medical libraries disclosed reports of only four cases previous to this one.

AUTHOR'S SUMMARY.

GIANT CELLS IN INFLAMMATIONS OF THE LUNG IN CHILDREN. ROBERT A. MOORE and PAUL GROSS, *Am. J. Dis. Child.* **40**:247, 1930.

At least four types of multinucleated cells are found in inflammations of the lung in children. Multinucleated cells may be formed by fusion of degenerated exudate, desquamated bronchial epithelium and desquamated alveolar epithelium. There is no evidence that pneumonia associated with multinucleated cells constitutes a distinct type. Extensive desquamation and giant cell formation may occur independent of alveolar exudation, and may be either a distinct type of alterative inflammation of the lung or a part of the pathologic changes of pneumonia alba. Giant cells in association with pneumonia have no specific cause.

AUTHORS' SUMMARY.

NEPHROSCLEROSIS (CHRONIC INTERSTITIAL NEPHRITIS) IN CHILDHOOD. A. GRAEME MITCHELL, *Am. J. Dis. Child.* **40**:345, 1930.

A comprehensive review of the subject of nephrosclerosis in children with special reference to renal rickets is presented. In his summary the author states that in studying the literature on nephrosclerosis, it is found that the terminology is confusing. The term chronic interstitial nephritis, which has been employed for a long time to describe the essential underlying pathologic process, is more descriptive of an end-result than of a definite entity. It is suggested that for the use of the clinician a simple terminology be adopted somewhat as follows: acute hemorrhage (glomerular) nephritis; acute edematous (tubular) nephritis (sometimes called nephrosis); chronic nephritis which is usually diffuse, but in which glomeruli, tubules, blood vessels or interstitial tissue may be involved to a greater extent than in the remainder of the kidney structure; suppurative nephritis which may be acute or chronic; lipid nephrosis. It would seem that all cases of actual disease of the kidney could be grouped etiologically, pathologically and symptomatically under such a classification. The term nephrosis, and especially lipid nephrosis, should be reserved for a relatively small number of cases in which there have been determined such well defined criteria as changes in the albumin-globulin ratio of the blood, increase in blood cholesterol and the demonstration of doubly refractile lipid bodies in the urine. Two cases of renal rickets and four cases of chronic nephritis in children are reported.

P. H. GUINAND.

CONGENITAL ATRESIA OF THE BILE DUCTS. A. MATHESON and I. HARRISON TUMPEER, *Am. J. Dis. Child.* **40**:571, 1930.

Congenital atresia of the bile ducts is one form of hepatic anomaly frequently encountered in earliest infancy. The symptoms are those of complete obstruction of the bile passages. The prognosis is bad in cases of complete atresia. When a diagnosis of complete biliary obstruction has been established, exploratory operation should be performed with the hope that the anomaly of the bile passages may be of such a nature that a communication with the intestines may be effected. A case of complete biliary atresia not amenable to surgical correction is here described.

AUTHORS' SUMMARY.

THE ORIGIN OF THE FIBROUS TISSUE ARISING IN THE TESTIS OF THE GUINEA PIG FOLLOWING EXPERIMENTAL TUBERCULOSIS. GEORGE A. BAITSELL and KARL E. MASON, *Am. Rev. Tuberc.* **21**:593, 1930.

Infection of the testicular tissues of the guinea-pig with tubercle bacilli causes rapid and marked degenerative changes of the germinal cells in the seminiferous tubules. The onset of these changes is more rapid in the testes of the reinfected animals than it is in the controls. The degeneration of the germinal cells is followed by their rapid elimination from the testes, which results in a marked decrease in the diameter of the tubules and a corresponding increase in the size of the intertubular areas. The rapid formation of an abundant exudate in the enlarged intertubular areas is a prominent feature of the histologic changes. The formation of fibrous tissue is brought about as the result of a direct transformation of the elements of the exudate in the intertubular areas. In the first stage there is a fine fibrillation with a typical appearance of a reticulum in the more advanced stage. The climax is reached in the formation of heavy bundles of wavy fibers identical with and staining for collagenous fibers. These fibers infiltrate and encapsulate the developing tubercles and, in general, permeate throughout the infected areas. The entire process of fibrous tissue formation is due to the fusion and consolidation of the minute filaments present in the exudate. This does not preclude the possibility that the infiltrating cells may alter the chemical nature of the developing fibrous tissue by means of cellular secretions, or the possibility that the movements of the cells through the exudate may, through mechanical factors, aid in bringing about the fusion of the fibrin-like elements present in the exudate. The development of the tubercles, which are characteristic of tissues infected with tubercle bacilli, in the infected regions of the testes takes place in the greatly enlarged intertubular areas following the exudate formation, cellular infiltration and development of the fibrous tissues.

H. J. CORPER.

PYLORIC OCCLUSION FROM SULPHURIC ACID. H. A. BRUCE, *Ann. Surg.* **92**: 897, 1930.

Complete pyloric inflammatory occlusion for a distance of 3 inches (7.6 cm.) resulted from the ingestion of 3 ounces (89 cc.) of sulphuric acid. Nine weeks after the accident, gastro-enterostomy showed a narrowed first and second portion of the duodenum. The dilated stomach showed only small hemorrhagic or fibrotic areas. The lips, mouth, pharynx and esophagus escaped serious damage. As is usual, in most cases the pyloric end of the stomach suffered most of the pathologic changes.

RICHARD A. LIFVENDAHL.

THE LIFE OF RETICULOCYTES. CLARK W. HEATH and GENEVA A. DALAND, *Arch. Int. Med.* **46**:533, 1930.

Reticulocytes in vitro at 37 C. and in the pleural cavity of the rabbit decrease at a regular rate over a period of from one to four days. This rate is analogous to a death rate or a maturation rate. The rate is similar for reticulocytes from various sources; for example, from bled rabbits, from those into which phenylhydrazine is injected and from cases of hemolytic jaundice and pernicious anemia. The rate is much slower at 23 C. or at 10 C. than at 37 C. Reticulocytes have been found in blood kept in the icebox for six months. The decrease in the number of reticulocytes is not related to degenerative changes which may take place in the blood in vitro. No dependable conclusion regarding the maturation rate of reticulocytes can be drawn from the experiments on the transfusion of reticulocytes into rabbits, but the results are not inconsistent with the observations concerning their decrease in the test tube. As the reticulocytes decrease in number in vitro, cells with "granules" progressively increase. Reticulocytes having large amounts of reticular substance are less mature than those having small amounts of reticular substance and require a longer period of time to reach maturity. There is an undoubted analogy between the rate of decrease in the

number of reticulocytes in vitro and of those in the blood stream. In both instances this is probably true maturation. Evidence strongly in favor of this conclusion is given by studies on reticulocytes from the blood of patients with pernicious anemia during the reticulocyte responses following liver therapy.

## AUTHORS' SUMMARY.

MYATONIA CONGENITA: WITH PARTICULAR REFERENCE TO PATHOLOGY AND FAMILIAL TENDENCY. E. S. GURDJIAN, Arch. Neurol. & Psychiat. **24**:52, 1930.

Of four patients with myatonia congenita (amyotonia or Oppenheim's disease) studied, one, a child aged 2½ years, died of bronchopneumonia. There were a paucity of ganglion cells in the anterior horns of the spinal cord, swelling with dislocation of the nuclei to the periphery and, in many cells, a lack of Nissl bodies. These changes were especially marked in the dorsolumbar region and were present also in Clarke's column. The anterior roots, especially of the lumbar region and the cauda equina, were atrophied and poor in myelin substance. The muscles—gastrocnemius and iliopsoas—also appeared atrophied and pale; the "interstitial nuclei" were increased, with perivascular infiltrations of lymphocytes and plasma cells. The heart showed subendocardial, fatty, degenerative infiltration, and lymphocytes and plasma cells were present in the "subserous material." The rest of the organs showed no noteworthy changes. Gurdjian concludes that myatonia congenita is akin to the Werdnig-Hoffmann type of muscular atrophy but is a less advanced stage of a lesion of the central and peripheral nervous systems, and that it may occur long after birth and be due to an infection or intoxication of the neuromuscular system (anterior horn cells, anterior nerve roots and striated muscle).

G. B. HASSIN.

NIEMANN-PICK'S DISEASE. GEORGE B. HASSIN, Arch. Neurol. & Psychiat. **24**:61, 1930.

The macroscopic and microscopic changes in a case of Niemann-Pick's disease much resembled those seen in the infantile type of amaurotic family idiocy (Tay-Sachs' disease); the brain was hard and leathery to the touch; the sylvian and interparietal fissures were gaping, and the frontal convolutions were markedly atrophied; the corpus callosum was thin; the ganglion cells appeared large and honeycombed; their nuclei were peripherally located and the apical dendron, like the cell body, was swollen. Few Nissl bodies were present in the expanded cell body, where they gathered around the nucleus. In some areas, the optic thalamus, for instance, these bodies were lacking. The contents of the cell body, its reticular cytoplasm, stained dark with any hematoxylin method and pale orange with scarlet red and appeared dustlike when stained with the silver method of Bielschowsky or Schultze-Stöhr. Other cells, also honeycombed but without processes, stained bright red with scarlet red, and these fat granule bodies were especially gathered around the blood vessels. Neurofibrils were few and were always pushed to the periphery. The same type of changes were seen in the cerebellum. The Purkinje cells were practically absent or greatly changed and were for the most part replaced by so-called "foam" cells and dense glia fibers. The optic thalamus was also markedly changed and like the cerebellum was transformed into a glia tissue scar. The "foam" cells, so typical of Niemann-Pick's disease, were also present in the arachnoid membrane, the ependyma of the sylvian aqueduct and the pineal body, and resembled the "foam" cells which were found in the rest of the body (liver, kidney, spleen, etc.). The changes in this condition are more advanced than those in amaurotic family idiocy (Tay-Sachs' type), and with the latter belong to a group of some metabolic disorder. However, it is hardly the same disease, for visceral changes described in Niemann-Pick's disease do not occur in amaurotic family idiocy, nor do all cases of Niemann-Pick's disease exhibit cerebral changes typical of amaurotic family idiocy.

AUTHOR'S ABSTRACT.

HYALINE DEGENERATION IN DEMENTIA PARALYTICA. ABNER WOLF, Arch. Neurol. & Psychiat. **24**:71, 1930.

In a patient, aged 48, who died of dementia paralytica, the frontal lobe exhibited a somewhat softened area, 2 cm. in diameter and extending 3 cm. deep, in the upper portion of the left precentral gyrus. The affected area consisted of a glassy material of almost "cartilaginous toughness"; smaller areas of similar structure occupied the occipital lobes, the second left temporal gyrus, both gyri recti and the thalamus. The rest of the tissues exhibited changes typical of dementia paralytica. The colloid mass appeared granular and argentophilic and, when stained with the various methods, proved to be a hyaline and carminophile substance. Many blood vessels showed a beginning deposit of hyalin in their walls, while other vessels were free or showed extensive and intensive hyalinization. Such areas exhibited large homogeneous macroglia cells and permitted study of the evolution of the process of hyalinization of the cortex, the various stages of the deposits of hyalin, the reaction of the surrounding tissues and the ultimate fate of the cerebral parenchyma. The conclusions Wolf arrived at are that in dementia paralytica disturbance of protein metabolism occurs; the walls of the vessels form the first barrier, being the first site of deposition of the abnormal material; the second defense mechanism is a ring of inflammation and reaction of macroglia; when the latter becomes insufficient, hyalin is precipitated; this results in destruction of the nervous parenchyma and formation of a status spongiosus (as a result of absorption of the deposits of hyalin).

G. B. HASSIN.

SUBARACHNOID HEMORRHAGE AS A CLINICAL COMPLICATION OF NEUROSYPHILIS. IRVING J. SANDS, Arch. Neurol. & Psychiat. **24**:85, 1930.

Hemorrhages in the brain or cerebral meninges are rarely encountered in neurosyphilis. Endarteritis or meningitis is more common. In one of the two cases reported of headache, pain in the occiput, drowsiness or unconsciousness with blurring of disks and bloody spinal fluid, a hemorrhage was found at the base of the brain, in the middle and posterior fossae. It surrounded the midbrain, pons, medulla and cerebellum. On the vertex of the brain, the pia-arachnoid showed extensive bloody infiltrations over the frontal and parietal areas. The fourth ventricle and some portions of the subarachnoid space were filled with blood. There was pial syphilitic endarteritis, and the cortical vessels were infiltrated with lymphocytes and plasma cells. The parenchymatous changes were mild, though the glial reaction in the cortex was intense. No hemorrhages were found within the brain substance proper. Sands concluded from his study that subarachnoid hemorrhages occurring in neurosyphilis are probably caused by rupture of diseased blood vessels of the pia.

G. B. HASSIN.

CHANGES OF THE SPINAL CORD IN HODGKIN'S DISEASE. PHILIP T. SHAPIRO, Arch. Neurol. & Psychiat. **24**:509, 1930.

The changes in the spinal cord in two cases of Hodgkin's disease are described. In the first, that of a colored woman, aged 32, with flaccid paralysis, there was an extensive infiltration of the spinal dura and the posterior nerve roots, with degenerative changes in the adjacent cord. In the second case, also in a woman, aged 30, there was a flaccid paralysis of the lower extremities with changes in the spinal cord somewhat similar to those in subacute combined cord degenerations.

G. B. HASSIN.

HUMAN BITE INFECTIONS OF THE HAND. M. L. MASON and S. L. KOCH, Surg. Gynec. & Obst. **51**:591, 1930.

Infection of the dorsal surface of the hand and phalanges as the result of teeth penetrating the skin and underlying structures causes a definite clinical and pathologic picture. In most cases the infection is of a mixed type from the onset,

although the fusiform spirillum is frequently found and is accountable in part for the foul-smelling and gangrenous lesions that so frequently occur. Recurrent "flare-ups" of the infection after incision are attributed to anaerobic organisms which reach sufficient growth in from four to five weeks to produce symptoms. Experimental injections demonstrate that the infection is likely to extend (1) lateralward in the subcutaneous tissues; (2) under the digital fascia of the proximal phalanx and around the finger; (3) more deeply, distalward along the proximal phalanx under the extensor tendon, with subsequent periosteitis and osteomyelitis; (4) under the extensor tendons and fibrous tissue; (5) into the middle palmar or thenar space by way of the lumbrical canal; (6) through the joint into the palm, under the volar interosseous fascia and then into the middle palmar or thenar space, and (7) into the synovial sheath and flexor tendons by erosion of the fibrous flexor tendon sheath.

RICHARD A. LIFVENDAHL.

EFFECTS OF THE ELECTROCAUTERY ON NORMAL TISSUES. J. GOTTESMAN, D. PERLA and J. M. ZIEGLER, *Surg. Gynec. & Obst.* **51**:667, 1930.

A comparative study of the manner and rate of repair of incisions aseptically produced by scalpel and those by desiccating knife of the electrocautery is reported. It was found that the latter produces extensive necrosis which acts as a foreign body with a resulting foreign body giant cell reaction in the skin, muscle, liver, kidney and spleen. These wounds heal more slowly and tend to suppurate more frequently than those made by the scalpel. It is also suggested that in cases of malignant tumors, cauterization seals the lymphatics, but that subsequent absorption is not decreased, because the lymph channels rapidly regenerate in granulation tissue. Secondary hemorrhage is also an inherent danger.

RICHARD A. LIFVENDAHL.

THE PATHOLOGICAL CHANGES FOUND IN A FATAL CASE OF PSITTACOSIS. G. HASWELL WILSON, *J. Path. & Bact.* **33**:957, 1930.

The general picture is that of septicemia accompanied by distinctive changes in the lungs. These are, in the order of their occurrence, congestion with abundant serous exudation, which ultimately becomes fibrinous; degeneration and desquamation of the epithelium lining the air vesicles and bronchi; thrombosis of the capillaries, or actual necrosis of the walls of the air vesicles in areas in which the damage is more severe, with hemorrhage in places. A relative absence of polymorphonuclear leukocytes is a striking feature and is consistent with the leukopenia observed clinically and with the microscopic appearances of the bone marrow.

FROM AUTHOR'S SUMMARY.

PERSISTENT EOSINOPHILIA. A. M. DRENNAN and J. H. BIGGART, *J. Path. & Bact.* **33**:995, 1930.

A case of persistent eosinophilia with splenomegaly and massive infiltration of the iliopsoas muscles is described. A suggestion is made that the syndrome "persistent eosinophilia and splenomegaly" may possibly be a functional disease—an expression of an excessive response on the part of the eosinophil to some as yet unidentified irritant.

AUTHORS' SUMMARY.

NECROTIC SEQUESTRATION OF THE KIDNEYS IN PREGNANCY. WALTER DE M. SCRIVER and HORST OERTEL, *J. Path. & Bact.* **33**:1071, 1930.

Necrotic sequestration of the kidney in pregnancy is the result of a terminal arterial segmentary collapse (vasoparalysis) with blood stasis and segmentary thrombosis with proximal extensions. The sequestered areas are immediately

surrounded by vessels still in "prestasis" and further on in "peristasis." These renal vascular disturbances seem to be related to a general abnormal state of vasomotor irritability of the pregnant state (hypertension) which provincially is functionally and anatomically revealed in the skin and in parenchymatous organs, notably the brain, liver and kidneys (edema, exudation, hemorrhages and necrosis). Based on these and similar anatomic observations elsewhere (uremic ulcers, eclamptic livers and lesions of the spleen and brain) and on experimental evidence as regards irritative circulatory changes in the living warm-blooded animal, it seems that the assumption of a paralytic terminal segmentary circulatory downfall (peristasis, prestasis, stasis) is in better harmony with these observations than the idea of vascular spasm and ischemia. Moreover, it furnishes a more definite mechanical conception of these lesions than the various rather hazy theories of primary "toxic cell degenerations." The very high intravascular fat contents of some of these cases suggest an associated hyperlipemia. It appears from the records of other published cases that a similar circulatory collapse with thrombosis may occur in certain infectious diseases for similar reasons.

AUTHORS' SUMMARY.

COAL-MINER'S LUNG. S. LYLE CUMMINS and A. F. SLADDEN, *J. Path. & Bact.* **33**:1095, 1930.

The black material in anthracotic lungs consists chiefly of coal dust. Iron is not an important constituent. Silica is found in anthracotic lungs in abnormal amounts. The pathologic effect of silica is to damage and block the lymph channels, so impairing the normal power of the lungs to dispose of inhaled dust. Whenever coal dust is retained in large amounts there is found also a high silica content in the lungs. Anthracosis of the lungs is determined by a combination of silicotic fibrosis and accumulation of coal dust. A considerable degree of anthracosis is consistent with working health. Coal miners especially exposed to silica dust are liable to develop a silicosis which, complicated by the effects of accumulation of anthracotic dust, may lead to disablement and death.

AUTHORS' SUMMARY.

CHANGES IN THE HEAD OF THE FEMUR IN SENILE DISEASE OF THE HIP. R. DE JOSSELINE DE JONG, *Virchows Arch. f. path. Anat.* **275**:348, 1930.

The condition to which the author devotes his attention develops slowly, without fever or disturbance of the general health, in the later years of life and leads to pain on and difficulty in walking. It is usually unilateral. It may begin at 32 to 35 years of age. It has been considered by some a form of arthritis deformans, although the proliferative reaction of the latter disease is absent. By some pathologists it has been termed chronic dry ulcerative arthritis of the hip. Jansen, on whose views the author draws freely, held the primary factor to be congenital flattening of the acetabulum. Jansen treats the condition by resection of the head of the femur. It is the femoral heads of six patients operated on by Jansen that de Jong describes in detail. The head is shorter and flatter than normal, and is more oval than round in shape. The free margin of the head is much more prominent than normal, and overrides the neck like a roof; it is this prominence of the margin that interferes with the gait. The round ligament is absent or atrophic. The cartilage of the convex portion of the head is eroded, and the exposed bone is hard and polished. On microscopic examination, the superficial lamellae and trabeculae of the bone of the femoral head were found to be denser than normal, compressed and closely applied to each other. There was no evidence of active resorption of bone by osteoclasts. The process is a degenerative and atrophic one. The deformity of the head of the femur results from pressure on bone the plasticity of which causes the bone to yield to the pressure. Concerning changes in the acetabulum or earlier stages of the process in the head of the femur, the author can express no opinion.

O. T. SCHULTZ.

PROGRESSIVE DESTRUCTION OF VERTEBRAE. M. B. SCHMIDT, *Virchows Arch. f. path. Anat.* **275**:373, 1930.

Schmidt describes an unusual condition of progressive destruction of the vertebral bodies, which he ascribes to trauma, and which may therefore be of considerable medicolegal interest. The patient was a man, aged 32, who had complained of pain in the back for two years previous to his death. The final clinical diagnosis, based in part on roentgenographic evidence, was compression myelitis due to multiple tumor metastases of the vertebral column. At necropsy it was found that the tenth dorsal vertebra had disappeared, and that the eleventh vertebra had been reduced to a thin, wedge-shaped structure. The third, seventh, ninth and twelfth dorsal vertebrae revealed distortion of the end-plates of the vertebral bodies, swelling and slight laceration of the intervertebral disks and microscopic changes that Schmidt believes explain the more severe involvement of the tenth and eleventh vertebrae. The end-plates of the twelfth vertebra were partly broken and displaced into the spongy bone of the body of the vertebra. Small islands of cartilage were present in the bone beneath the end-plates. Such a misplacement of cartilage, which Schmorl has described as of frequent occurrence in apparently normal persons, the latter author has ascribed to the mechanical trauma of ordinary locomotion. The trabeculae of the spongy bone at the center of the twelfth vertebra were fractured, necrotic and in the process of resorption. There were hemorrhage and connective tissue reaction in this portion of the vertebral body. According to Schmidt, the disintegration, necrosis and resorption of spongy bone, once initiated, became a continuing process, which led to the complete disappearance of a vertebral body. The process described by Schmidt is unlike the progressive atrophy of vertebral bodies discussed by Schmorl and others. It has a striking similarity to the posttraumatic vertebral disease of Kümmell. In the latter, however, the destructive process is limited to a single vertebral body, and there is usually a history of trauma, which is less severe than that required to cause a true vertebral fracture. In Schmidt's case no history of trauma to the spine could be elicited, but the author believes the lesion to have been the result of a mechanical trauma of so slight a grade that it escaped the patient's attention.

O. T. SCHULTZ.

LIPOIDAL AND OXYDASE GRANULES IN THE LEUKOCYTES OF THE PERIPHERAL BLOOD. W. S. NESTEROW, *Ztschr. f. d. ges. exper. Med.* **72**:256, 1930.

Methods are described by which two varieties of monocytes may be recognized in the peripheral blood. They have different biologic functions and different staining reactions. One type, which in function seems to be related to reticulo-endothelium, takes up fragments of neutrophils, erythrocytes and lymphocytes, and does not contain lipid granules. These cells are not found normally in the peripheral blood. The second type is present in normal blood of human beings and dogs and contains lipoidal and oxydase granules. In certain pathologic conditions the granules are increased in number.

PEARL ZEEK.

SPONTANEOUS PNEUMOTHORAX CAUSED BY LYMPHOGRANULOMA. R. I. KOTTLER, *Ztschr. f. Tuberk.* **58**:37, 1930.

A woman, 23 years old, showed at necropsy mediastinal and pulmonary lymphogranuloma, a spontaneous pneumothorax and a rupture into the esophagus, produced by specific lesions.

MAX PINNER.

## Microbiology and Parasitology

ACUTE SUPPURATIVE THYROIDITIS IN CHILDREN. J. M. MORA, Am. J. Dis. Child. **40**:500, 1930.

Two unusual cases of acute suppurative thyroiditis in children, aged  $2\frac{1}{2}$  and 13 years, respectively, with operative recovery, are recorded. In both cases the primary infection was a sore throat, and in both instances the offending organism was a hemolytic streptococcus.

AUTHOR'S SUMMARY.

NITRITE REACTION AS A DIAGNOSTIC TEST IN INFLUENZAL MENINGITIS. ROY M. GREENTHAL, Am. J. Dis. Child. **40**:569, 1930.

A positive nitrite reaction with the spinal fluid was obtained in thirteen consecutive cases of influenzal meningitis, and was always absent in meningococcic, tuberculous and streptococcic meningitis. The nitrite test, according to the method described, may be used as a rapid corroborative test for the diagnosis of influenzal meningitis.

AUTHOR'S SUMMARY.

INFECTIOUS MONONUCLEOSIS. J. P. PRICE, Am. J. Dis. Child. **40**:581, 1930.

A case of infectious mononucleosis in a baby, aged 7 months, is reported with a general discussion of the disease. Especial reference is made to the difficulty in diagnosis between infectious mononucleosis and acute lymphatic leukemia in the early stage.

AUTHOR'S SUMMARY.

INTESTINAL PROTOZOA OF MONKEYS AND MAN. ROBERT HEGNER and H. J. CHU, Am. J. Hyg. **12**:62, 1930.

The objects of this investigation were to determine whether wild monkeys are parasitized with intestinal protozoa as captive monkeys are known to be, and to compare these protozoa with species that occur in man with special reference to specific identity. The digestive tract of forty-four wild Philippine monkeys of the species *Macacus philippinensis* (twenty-eight males and sixteen females) was examined immediately, or within three hours, after death; the vaginas of the females were also examined. The data recorded in this paper furnish evidence that is considered insufficient to separate as distinct species the eleven types of protozoa described from wild Philippine monkeys and the corresponding eleven types that live in man.

AUTHORS' SUMMARY.

EPIZOOTIC FOX ENCEPHALITIS. R. G. GREEN, Am. J. Hyg. **12**:109, 1930.

A summary is presented of the physical signs and symptoms, histologic observations, etiology, transmissibility and immunology of epizootic fox encephalitis in 125 foxes.

P. H. GUINAND.

THE SUSCEPTIBILITY OF AFRICAN MONKEYS TO YELLOW FEVER. JOHANNES H. BAUER and ALEXANDER F. MAHAFFY, Am. J. Hyg. **12**:155, 1930.

Attempts were made to infect African monkeys of four different species, *Cercopithecus tantalus*, *Cercopithecus mona*, *Cercocebus torquatus* and *Erythrocebus patas*, with yellow fever, both by the injection of virulent blood from infected rhesus monkeys and by the bite of infected *A. aegypti*. None of the animals succumbed to infection with yellow fever, but for a number of days the virus persisted in the blood of all except *Cercopithecus mona*, and it could be recovered again by the injection of their blood into susceptible rhesus monkeys. Two of the species, *Cercopithecus tantalus* and *Cercocebus torquatus*, were found definitely

capable of transmitting the infection to normal *A. aegypti*; the results with *Erythrocebus patas* in this respect were suggestive, but not definite, and no attempts were made to infect mosquitoes from *Cercopithecus mona*. Five monkeys, representing three different species, were bled before and after the experimental infection; the specimens of serum taken before the infection showed no protective properties, whereas those taken afterward protected rhesus monkeys, in 5 cc. amounts, against a relatively large dose of the virus.

AUTHORS' SUMMARY.

STUDIES ON THE FILTRABILITY OF YELLOW FEVER VIRUS. JOHANNES H. BAUER and ALEXANDER F. MAHAFFY, Am. J. Hyg. **12**:175, 1930.

Yellow fever virus, both in the blood of infected monkeys and in infected mosquitoes, was found to pass through Berkefeld filters of all grades without a marked diminution in concentration, and also through Chamberland L-11 candles. No evidence was found to indicate that virus in blood differs from that in mosquitoes. The virus dies out rapidly when suspended in 0.9 per cent solution of sodium chloride, Locke's solution, Ringer's solution, hormone broth or distilled water; but it was found that when 10 per cent or more of normal rhesus serum is added to saline or distilled water, the deleterious effect of these mediums on the virus is much reduced.

AUTHORS' SUMMARY.

A REPORT ON A CASE OF GIARDIASIS. H. TSUCHIYA and JUSTIN ANDREWS, Am. J. Hyg. **12**:297, 1930.

The pathogenicity of *Giardia lamblia* is still open to question. The present report represents one instance in which the flagellate seems to have played a pathogenic rôle.

AUTHORS' SUMMARY.

THE RÔLE OF THE LEUCOCYTES IN TUBERCULOSIS. BENJAMIN L. BROCK, Am. Rev. Tuberc. **21**:745, 1930.

Periodic studies of the total and leukocytic counts often give a truer picture of the tuberculous condition than does the clinical course of the case. The neutrophil plays the part in the formation of tuberculous abscesses. Elevation in the percentage of neutrophils over a period of time is indicative of breaking down of tissue with the formation of abscesses. The total count, with the percentage of neutrophils, denotes the degree of activity. The lymphocyte plays the important rôle in the healing of the lesion. A definite increase in the percentage of lymphocytes, when the neutrophils remain around normal over a given period, is indicative of healing. In such cases the monocytes are found within normal limits. The monocyte plays the chief rôle in new tubercle formation. Elevation in the percentage of monocytes is rather consistent in cases showing a definite elevation in the percentage of neutrophils. Such a picture indicates spread of the disease with the formation of abscesses. Clinically active tuberculosis and progressive pathologic disease respond with septic types of leukocytic pictures. No definite rôle has as yet been ascribed to the eosinophil or the basophil.

H. J. CORPER.

THE LEUCOCYTIC INTERPRETATION OF MEDLAR IN TUBERCULOSIS. WILLIAM H. OATWAY, JR., Am. Rev. Tuberc. **21**:786, 1930.

The scheme and limits of Medlar prove more sensitive than any other classification available when other causes of leukocytosis are absent in a tuberculous person. An excess of neutrophils, the septic picture, indicates the most severe and dangerous process. An increase in monocytes in an otherwise normal count, the hyperplastic type, is a more favorable passive type. The normal, inactive, leukocytic picture is evidence that the lesion is being well controlled. An increase of lymphocytes, giving the resistant picture, indicates a healing lesion. Eosinophils

and basophils had no demonstrable relation to the progress or severity of the cases. The types used in the interpretation by Medlar seem sufficient when intelligently used to show the action of the whole pathologic process. H. J. CORPER.

THE EFFECT OF ULTRAVIOLET IRRADIATION ON TUBERCULOUS PERITONITIS IN GUINEA PIGS. M. MAXIM STEINBACH, ALFRED F. HESS and MILDRED WEINSTOCK, *Am. Rev. Tuberc.* **22**:35, 1930.

When guinea-pigs are infected with mildly virulent tubercle bacilli intraperitoneally, extensive tuberculous disease develops, even though they are subsequently treated with ultraviolet irradiation. In the animals that received irradiation, tuberculosis developed to the same degree as in those that had not been treated with the ultraviolet rays, and in some instances they showed more extensive disease than did the controls.

H. J. CORPER.

CHEMICAL CHANGES FROM GROWTH OF BOVINE TUBERCLE BACILLI ON LONG'S MEDIUM. ALICE G. RENFREW, KATHERINE M. HARING and TREAT B. JOHNSON, *Am. Rev. Tuberc.* **22**:116, 1930.

The growth of bovine tubercle bacilli was followed for sixteen weeks. Carbohydrate combinations, as judged by the copper-reducing properties of the cultures, made their appearance after the third week of growth. The analytic values for reducing sugars after hydrolysis were much higher for bovine bacilli than for avian and timothy cultures, but less than half the value determined for the human strain, H37.

H. J. CORPER.

THE GROWTH-PROMOTING PRINCIPLE IN THE POTATO. NAO UYEI, *Am. Rev. Tuberc.* **22**:203, 1930.

Practically all of the active principles in potato for the growth of tubercle bacilli in vitro are to be found in the residue of the potato after its extraction with the common organic solvents, such as acetone, alcohol or ether. Investigation of the effects of the various elements known to be present in the potato revealed two classes of stimulants for the growth of tubercle bacilli. One class is represented by inositol, maltose and dextrose, and is termed metabolic stimulants, because the substances stimulate the growth of tubercle bacilli only when the bacilli are present in large numbers, while the other class of stimulant is represented by soluble starch and dextrin, and is termed reproductive stimulants, because the substances not only stimulate the growth of tubercle bacilli when these are present in large numbers, but also in small numbers. Glycogen does not appear to possess the property of stimulating the growth of tubercle bacilli in vitro, and future studies will be required further to elucidate this.

H. J. CORPER.

STREPTOTRICHOSIS. J. J. SINGER and HARRY C. BALLON, *Am. Rev. Tuberc.* **22**:233, 1930.

A case of streptotrichosis, possibly primary in the lungs, is reported. *Streptothrix* was found in the gums, sputum, pus from superficial abscesses and, at autopsy, in practically every organ of the body. Throughout the illness there was a persistent and unexplained purpura. The lesion in the lung was associated with pulmonary tuberculosis. Tubercle bacilli were demonstrated from direct smear in pus obtained from the abscess cavities, but at no time during the course of the disease could they be demonstrated in the sputum. The lesions in the lung showed the characteristic nodular formation with necrosis and the formation of abscesses. There were few proliferative changes and consequently little or no evidence of bronchiectasis. The character of *Streptothrix* in this case is reported separately.

H. J. CORPER.

PRIMARY ASPERGILLOSIS OF THE LUNGS. LEO V. SCHNEIDER, *Am. Rev. Tuberc.* **22**:267, 1930.

*Aspergillus fumigatus* produces pulmonary lesions resembling those of fibroid tuberculosis. Differential diagnosis is particularly difficult when aspergillus infection is secondary to any respiratory infection. Aspergillus infection is transmitted from pigeons and parrots, and is also observed in hair-combers who use rye flour to remove grease from the hair. Animals inoculated with spores from a pure culture of *Aspergillus fumigatus* showed typical lesions at autopsy. Tuberculin tests are of no diagnostic value because aspergillosis gives the same local reaction as tuberculosis. Iodides seem to be specifically destructive to the life and growth of the aspergillus fungus.

H. J. CORPER.

STUDIES IN BACTERIAL METABOLISM. A. I. KENDALL, T. E. FRIEDEMANN and M. ISHIKAWA, *J. Infect. Dis.* **47**:186, 1930.

"Resting" bacteria are defined as organisms that are fully mature and endowed with their full potentiality for metabolism, but constrained from multiplication by the withholding of substrates essential for their continued growth. It is inferred, therefore, that "resting" bacteria initiate changes in substrates that they, as proliferating bacteria, will subsequently use for their energy requirements. The details for cultivating, harvesting and testing the chemical activity of suspensions of "resting" bacteria are discussed in detail. Quantitative studies of the action of suspensions of certain representative bacteria were made, dextrose, lactic acid, pyruvic acid and alanine being used as substrates, singly and in combination, in the presence and absence of oxygen, and in the presence and absence of methylene blue (methylthionine chloride, U. S. P.). The determinations comprised the quantitative partition of these substances under the various conditions enumerated, together with the quantitative determinations of volatile acids and carbon dioxide. The outstanding facts were as follows:

Bacteria that ferment dextrose habitually, as *Bacillus coli*, *B. pyogenes-foetidus* and *Staphylococcus aureus*, as "resting" bacteria, transformed dextrose rather vigorously. There was a concomitant but not an equimolecular increase in lactic acid.

Bacteria that do not utilize dextrose, as *B. alcaligenes* and *Vibrio* H/61, did not, as "resting" bacteria, induce a measurable change in the dextrose molecule.

*B. pyocyaneus*, which ferments dextrose less readily than most bacteria in the "resting" state, decomposed this substance readily in the presence of oxygen. In the absence of oxygen, practically no dextrose was transformed.

Pyruvic acid was energetically decomposed by the bacteria that fermented dextrose. *B. pyocyaneus*, which is not an active fermenter of dextrose, transformed pyruvic acid rather vigorously. In the absence of oxygen, "resting" *B. pyocyaneus* decomposed pyruvic acid, even though dextrose was not attacked under anaerobic conditions. It is surmised, therefore, that pyruvic acid is formed when "resting" bacteria are acting on dextrose, but fails to accumulate because it is utilized nearly as rapidly, during the process of fermentation of dextrose.

Nonfermenting bacteria, exemplified by "resting" *B. alcaligenes* and *Vibrio* H/61, failed to produce a discernible change in pyruvic acid.

Lactic acid was decomposed by all the bacteria studied. Generally speaking, the loss in lactic acid was greater in the presence than in the absence of oxygen. It appears to be significant that "resting" *B. alcaligenes* and *Vibrio* H/61 transformed lactic acid nearly quantitatively to pyruvic acid. These bacteria did not ferment dextrose. On the other hand, the fermenting bacteria, previously enumerated, although transformers of lactic acid, failed to record a proportionate increase in pyruvic acid. As pyruvic acid disappeared rapidly in the presence of "resting" bacteria of the fermenting type, it is possible that it was formed and transformed at nearly equal rates.

Alanine was not a particularly favorable substrate for the fermenting bacteria. However, *B. alcaligenes* appeared to transform it fairly readily.

It is suggestive, if not significant, that both gas-producing and nongas-producing fermenting bacteria exhibit qualitative similarity in their respective activities as "resting" bacteria on the substrates examined, especially dextrose and pyruvic acid. The aerogenic organisms, exemplified by "resting" *B. coli*, appear to initiate the attack on the dextrose molecule in the same manner as the nonaerogenic fermenting bacteria, exemplified by "resting" *B. pyogenes-foetidus* and *Staphylococcus aureus*. Therefore, the exuberant production of gas (hydrogen and carbon dioxide) would seem to be a terminal reaction, not manifested by "resting" bacteria.

In the presence of oxygen, methylene blue appears to increase somewhat the action of "resting" bacteria, both of the fermenting and of the nonfermenting type, on lactic acid. In the absence of oxygen, the transformation of lactic acid is materially increased; even the nonfermenting type, as *B. alcaligenes*, decomposes considerable lactic acid in the presence of methylene blue, but in the absence of oxygen. As pyruvic acid is formed in the latter instance, it is assumed that suspensions of "resting" *B. alcaligenes* dehydrogenate lactic acid to pyruvic acid, thereby becoming hydrogenated. Methylene blue dehydrogenates the "resting" bacteria in turn, becoming reduced thereby to leukomethylene blue. There is evidence that methylene blue exerts some harmful influence on "resting" bacteria.

"Resting" bacteria of the dextrose-fermenting type, exemplified by suspensions of *B. coli*, *B. pyogenes-foetidus* and *Staphylococcus aureus*, appear to transform at least some pyruvic acid to lactic acid. Nonfermenting types, for example, "resting" *B. alcaligenes* and *Vibrio* H/61, have little action on pyruvic acid; in fact, the reaction proceeds nearly quantitatively in the opposite direction, lactic acid to pyruvic acid. As the transformation of pyruvic acid is reminiscent of the action of the tissue enzyme, glyoxalase, which transforms methylglyoxal, an aldehyde corresponding to pyruvic acid, to lactic acid, it was surmised that the two processes might be somewhat analogous. Experiments made with "resting" bacteria indicate that those organisms in the "resting" state which do ferment dextrose have a distinct glyoxalase-like action. Those which fail to transform dextrose, and which also fail to act on pyruvic acid, are devoid of glyoxalase-like action. It was also shown that suspensions of "resting" bacteria cultivated for considerable periods of time in the presence of dextrose have, as "resting" bacteria, distinctly more intense glyoxalase-like activity than suspensions of corresponding strains developed in the absence of dextrose. The magnitude of chemical change induced by the fermenting strains, which stands in distinct contrast to the inactivity of the nonfermenting strains measured under parallel conditions, would appear to justify the general conclusion that the former (dextrose-fermenting) organisms in the "resting" state exhibit definite glyoxalase activity, whereas the latter (nondextrose-fermenting) organisms in the "resting" state are devoid of glyoxalase activity.

#### AUTHORS' SUMMARY.

#### THE UTILIZATION OF CERTAIN SUBSTITUTED CARBOHYDRATES BY BACTERIA. A. I. KENDALL and C. E. GROSS, *J. Infect. Dis.* 47:249, 1930.

This investigation is a qualitative study of the effect of definite alteration in certain carbohydrate molecules on their utilization by specific bacteria. The series of compounds considered included derivatives of d-dextrose, d-mannose and fructose of the hexose series, d-galactose, d-arabinose and l-arabinose, d-xylose and glycerin. The most significant fact deduced was that any departure from the configuration of the d-dextrose molecule decreases its utilizability by common bacteria. Oxidation of d-dextrose to gluconic acid or to glucuronic acid is less potent in reducing utilizability than reduction of the d-dextrose molecule to sorbitol. Substitution of from one to four methyl groups in the molecule makes the resulting compound refractory to microbial attack. The same generalization holds for mannose and galactose, except that mannitol, the alcohol of d-mannose, is distinctly more utilizable than sorbitol, the alcohol derivative of d-dextrose. Galactose is fermented by a greater variety of bacteria than either mannose or fructose. In this respect it appears to stand next to dextrose. This is significant in light of

the fact that galactose does not have a common enol with dextrose; formerly it was held that hexoses having a common enol are mutually fermentable. In this connection, the nonfermentability of gamma trimethyl xylose, chemically a very reactive sugar, is of interest as suggesting that even intense chemical reactivity is not of itself a criterion on which to predicate biologic utilizability. An unexpected instance of protoplasmic versatility seems to be shown in the mutual fermentation of d-arabinose and its precise opposite, l-arabinose. In light of current views of protoplasmic orientation and polarity, this observation is unexplainable, and should be repeated.

## AUTHORS' SUMMARY.

## THE PRODUCTION OF HISTAMINE BY CERTAIN STRAINS OF THE GAS BACILLUS.

A. I. KENDALL and E. GEBAUER, *J. Infect. Dis.* **47**:261, 1930.

Histamine was isolated as the picrate from milk cultures of a strain of the gas bacillus. The analysis of the picrate for carbon, hydrogen and nitrogen was in reasonable accord with theoretical values. Further identification of this picrate was had from the Pauly reaction, and the physiologic action on smooth muscle, both qualitatively and quantitatively. Only certain strains of the organism produce histamine.

## AUTHORS' SUMMARY.

## A STUDY OF BACTERIUM DYSENTERIAE, SONNE TYPE. S. A. KOSER, D. O.

REITER, E. BORTNIKER and E. I. SWINGLE, *J. Prev. Med.* **4**:477, 1930.

The Sonne dysentery bacilli appear to constitute a distinct type on the basis of both physiologic characteristics and agglutinative relationships. The nineteen Sonne cultures included in the present study possessed the property of fermenting the following sugars with production of acid: dextrose, lactose (slow), sucrose (slow), usually raffinose (slow), arabinose, rhamnose, levulose, mannose, galactose, maltose, trehalose, mannitol and glycerol. Negative results occurred with xylose, melezitose, dulcitol, sorbitol, adonitol, erythritol, salicin and inulin. It is probable that dextrin is only sparingly utilized, if at all. All the Sonne cultures gave negative results in tests for the formation of indol, showed no liquefaction of gelatin or digestion of starch and gave no evidence of the production of hydrogen sulphide in a dextrose agar sulphite ferric chloride medium. Nitrates were reduced to nitrites. A number of other dysentery-like organisms described under a variety of names were found to be identical with the Sonne type in every respect. One of the most striking characteristics of the Sonne cultures was the slow production of acid from lactose and sucrose—a property shared by certain other, miscellaneous cultures, including the dispar type. The two dispar cultures studied in this investigation differed from the Sonne strains in their ability to attack xylose and sorbitol and to form indol. They were also distinct serologically. Both types may be readily distinguished from the Flexner organisms. A review of the recorded isolations of the Sonne type shows that it has been found in many localities in association with dysentery or dysentery-like conditions, particularly those of infants.

## AUTHORS' SUMMARY.

BACTERIAEMIA FOLLOWING OPERATIONS ON THE URETHRA. F. J. F. BARRINGTON and HEDLEY D. WRIGHT, *J. Path. & Bact.* **33**:871, 1930.

Invasion of the blood stream by bacteria is a common occurrence following operations on the urethra, and this can be recognized within a few minutes after the operation. The organisms come from the urinary passages, and the invasion is conditioned in part by the numbers of organisms in the urine and in part by the facilities afforded for invasion by tissue damage. Similar invasion may occur later after natural micturition and may be of much higher grade. Fever and rigors do not necessarily follow such blood invasions but appear to depend on the size of the blood invasion. When a rigor occurs it is at an interval after the blood invasion, and at the time of the rigor the blood may be sterile.

## AUTHORS' SUMMARY.

INFLUENCE OF CALCIUM ON MICROBIC SPECIES. PAUL BORDET, Ann. de l'Inst. Pasteur **45**:26, 1930.

Deprivation of calcium profoundly modifies certain microbic species; e. g., it exaggerates sporulation regularly and in marked degree. A microbic species composed of two races, unequally sporogenous, shows, under the influence of oxalate medium, a predominance of the sporogenous variety. Calcium appears, then, to be one of the factors in microbic variation. It is, seemingly, a disturbance of this variability which explains the distinct increase in the chromogenesis of *Chromobacterium prodigiosum* under the influence of a lack of calcium. This determines, with certain bacilli, considerable morphologic variation, transforming them into short rods and often into coccobacilli. The modifications determined by the use of oxalate medium have as a distinctive feature the failure to produce any alteration in hereditary potentialities; replaced in contact with calcium, the organism immediately resumes its normal characteristics. This contribution furnishes nineteen figures in color.

AUTHOR'S SUMMARY.

A BACILLUS OF CUTANEOUS GANGRENE. R. NATIVELLE, Ann. de l'Inst. Pasteur **45**:169, 1930.

Milian's *Bacillus gangraenae-cutis* was isolated in fourteen cases of true cutaneous gangrene. The organism, which is completely described, is a gram-negative rod, with a tendency to bipolar staining; it shows motile, peritrichous flagella; it is nonsporulating and in older cultures it occurs as long filaments. It grows easily on the usual mediums, the optimum temperature being about 37 C. The organism is aerobic; it is also a facultative anaerobe. It produces a fetid odor. It survives some months in cultures. Biochemically, the results recorded are very irregular. In general, the organisms isolated were proteolytic, nonhemolytic in mediums and rather weakly saccharolytic. A definite toxin was not demonstrated. Agglutination and complement-fixation showed great variation and no group specificity, and no relationship to *Pseudomonas pyocyanea*, *Bacterium coli* or *Proteus vulgaris*, to which the organism might be related. Treatment with specific serum, as well as with specific intravenous injections of arsphenamine, is suggested (illustrated in an experimental lesion in a rabbit).

The pathogenicity is variable in degree. Though the organism is common and responsible for some histologic changes, the rôle is apparently that of a secondary invader. Post mortem, the gangrenous and ulcerative condition seems confined to the superficial layers, being never observed deep in the muscle. Histologically, a sharply delineated massive infiltration occurs, with the arterioles unaffected. A black pigment is deposited in the liver and the spleen. The lesions are duplicated in lesions induced experimentally in guinea-pigs or in rabbits. Subcutaneous injection of the organisms into guinea-pigs is followed by edematous swelling and purpuric spots. In forty-eight hours a blackish, well defined lesion appears, 5 or 6 cm. in diameter, which passes through various ulcerative stages to complete cure in from fifteen days to three weeks. The reaction is local (illustrated by plates). Similar lesions may be produced in rabbits, which respond, perhaps, more vigorously.

M. S. MARSHALL.

ONE OR SEVERAL RABIES VIRUSES. P. REMLINGER and J. BAILLY, Ann. de l'Inst. Pasteur **45**:376, 1930.

By analogy, there might be several types of rabies virus, as there are in the case of numerous bacterial agents of infection, or variations in these agents. Following suggestions made at the international conference on rabies (1927) cases have been noted in which apparent failure of cross-protection indicates discrepancies suggesting the existence of several strains of virus. A study of strains of virus from various locales in rabbits leads the authors to uphold the stability of a single virus, remarking, "If one uses in intensification and preservation (of the virus) a fraction

of the time which certain authors advocate spending in the preparation of polyvalent vaccines or autogenous vaccines, one will have no cause to regret it." A virus derived from an original Pasteur strain, now in its 2480th passage, regularly used by the authors at their Pasteur Institute in Tangiers, is cited.

M. S. MARSHALL.

THE CORRELATION BETWEEN TUBERCULOUS DISEASE AND THE GENERATIVE PROCESSES IN THE FEMALE ORGANISM. JOACHIM GRANZOW (Berlin: S. Karger, 1930).

This monograph with bibliography is a supplement to the *Monatschrift für Geburtshülfe und Gynäkologie*. The thesis is based on a comprehensive study of nonpregnant, pregnant and puerperal guinea-pigs infected with attenuated tubercle bacilli by way of the right ventricle. The conclusions are as follows: 1. The normal quiescent uterus has a marked resistance against hematogenous infection with tubercle bacilli, while in pregnancy and puerperium the uterus is more frequently involved. 2. Hematogenous infection, in the majority of cases, leads to abortion, premature labor or stillbirth.

Granzow considers the abortions to have been an expression of resistance to infection, but bacilli might readily have entered the intervillous spaces of the placenta. Nonspecific and severe degenerative changes of the ovarian parenchyma were frequently present, and interfered with ovulation. The ovarian changes ran parallel with the severity of the disease. The lymph glands were not as often tuberculous during pregnancy as in puerperium. The liver, spleen, kidneys, heart and mammary glands were more frequently involved in pregnant—especially during the puerperium—than in nonpregnant, animals. On the other hand, the lungs of the guinea-pig were more resistant to tuberculosis during the pregnant state. The functional changes of pregnancy in certain organs increased their disposition to tuberculosis, and this was true especially of the mammary glands. In resistance to tuberculosis, the endocrine glands were not, as a rule, severely affected by pregnancy.

A. J. KOBAC.

CULTURE OF THE TUBERCLE BACILLUS. M. MALKANI, Beitr. z. Klin. d. Tuberk. **73**:395, 1930.

Known amounts of tubercle bacilli were seeded on egg mediums according to Lubenau-Hohn, Petroff and Petragnani's medium. It was found that Lubenau-Hohn's medium and that of Petroff yielded equally good results, while Petragnani's medium was disappointing. The number of colonies in the latter always remained far below the number of seeded organisms.

MAX PINNER.

A CASE OF PULMONARY ASPERGILLOSIS. R. BERGMAN and F. HENSCHEN, Beitr. z. Klin. d. Tuberk. **73**:467, 1930.

A woman had the symptoms of a chronic pulmonary disease for twenty years. For the last ten years, in various hospitals, her condition had been diagnosed as far advanced pulmonary tuberculosis. The clinical course was very chronic, in spite of the extensive lesion, and the general condition of the patient remained fair, in spite of a major operation and a chronic renal disease. She had frequent hemoptysis. Tubercle bacilli were never demonstrable in the sputum. At necropsy a pulmonary infection with *Aspergillus fumigatus* was found. The molds were found chiefly in preformed cavities, and they did not show any tendency to infiltrative growth. The hemoptyses were probably caused by richly vascularized granulation tissue in the walls of cavities. A source of infection of the usual type was not demonstrable.

MAX PINNER.

CONGENITAL TUBERCULOSIS. M. ZARFL, Beitr. z. Klin. d. Tuberk. **74**:380, 1930.

A case of congenital tuberculosis is reported. Sixteen days after birth the tuberculin reaction was positive. Clinically the disease began with abdominal symptoms. The infant died when it was 39 days old. At necropsy a primary complex was found in the liver, with extensive caseation of the portal lymph nodes. The primary focus showed deposits of lime and fibrous encapsulation. The miliary tubercles in the lung were all of the exudative type.

MAX PINNER.

### Immunology

THE SENSITIZATION OF CATTLE TO TUBERCULIN BY OTHER THAN TUBERCLE BACILLI. E. G. HASTINGS, B. A. BEACH and ISABEL THOMPSON, Am. Rev. Tuberc. **22**:218, 1930.

A number of cultures have been isolated from the tissues, usually lymph nodes, of cattle which have reacted to tuberculin, but which have shown no evidences of the disease on postmortem examination. When injected into tuberculosis-free cattle, these cultures cause sensitization to tuberculin, which condition is, in most cases, evanescent. The cultures were proved free from tubercle bacilli before use in cattle through the injections of guinea-pigs, rabbits and fowl. The cultures produce no lesions in cattle. The observations indicate that a positive response to tuberculin in cattle is not absolute proof of infection with tubercle bacilli. Some other of the mycobacteria may invade the tissues and cause sensitization to tuberculin.

H. J. CORPER.

LOCAL IMMUNITY OF THE PERITONEUM. IRVING A. FRISCH, Arch. Int. Med. **46**:410, 1930.

A modification of the phenomenon of local skin reactivity introduced by Schwartzman is described in this report. This modification consists in the employment of an intraperitoneal instead of an intravenous injection of toxic substance twenty hours after such a preliminary inoculation into the skin. By means of this modification, the principle of local peritoneal immunity was demonstrated. Rabbits in which the intraperitoneal injection of *B. typhosus* culture filtrate was able to elicit the Schwartzman phenomenon in previously prepared skin sites were rendered negative to this phenomenon by repeated injections of this culture filtrate intraperitoneally. It was then shown that this reaction of the skin could still be produced if the reacting factors were introduced intravenously. It must thus be concluded that the immunity produced under these circumstances was of a distinctly local character involving only the peritoneum, and that the entire organism was not yet immune. It was also determined that between three and four injections of *B. typhosus* culture filtrate were necessary to render the peritoneum immune to this filtrate.

AUTHOR'S SUMMARY.

TRANSFUSION FROM A GROUP A DONOR TO A GROUP B RECIPIENT WITHOUT FATAL RESULT. LYMAN BURNHAM, Arch. Int. Med. **46**:502, 1930.

A full transfusion (400 cc. into a recipient weighing but 85 pounds) of group A blood into a group B recipient was accidentally performed, with only slight symptoms: coughing, oppression in the chest, slight dizziness and pain in the lumbar regions. The incompatible transfused blood remained in the circulation of the recipient for from three to five days. The absence of serious consequences was shown to be due to the fact that all of the group-specific iso-agglutinin  $\alpha$  in the recipient's serum was entirely incapable of clumping the group A cells of the donor at body temperature, although it clumped these cells vigorously at room temperature.

AUTHOR'S SUMMARY.

CHARACTERISTICS OF NATURAL AGGLUTININS. H. J. GIBSON, J. Hyg. **30**:337, 1930.

A study has been made of natural agglutination as exemplified by the reactions of the serum of nine animal species with a variety of bacteria.

AUTHOR'S SUMMARY.

HETEROPHILIC ANTIBODY IN HUMAN SERUM AND THE SKIN REACTION TO GUINEA-PIG SERUM. SUSAN GRIFFITH RAMSDELL, J. Immunol. **19**:341, 1930.

Guinea-pig serum, used as a native heterophilic antigen, occasioned reactions of the skin of the immediate type, with regularity, in a group of patients with disturbances of the skin believed to be allergic. In the normal group, this reaction appeared in about half the members. The presence of agglutinin for sheep cells was a regular finding in the allergic group in titers considerably higher than that found in the normal. The hemolysin titers did not vary with the groups. No correlation could be established between the occurrence of a reaction of the skin to guinea-pig serum and the heterophilic antibody titers. Suspensions of haptene and lecithin did not occasion a marked reaction in any instance. The submaximal response could not be correlated with any other observation. The response of the skin to guinea-pig serum could not be identified as a reaction between human heterophilic antibody and a native heterophilic antigen assumed to be contained in the guinea-pig serum.

AUTHOR'S SUMMARY.

MOLECULAR MOVEMENT, VISCOSITY AND AGGLUTINATION. STEPHEN WENT, J. Immunol. **19**:347, 1930.

The viscosity of the dispersing medium affects the Brownian movement of bacteria a great deal. Above a certain degree of internal friction, molecular movement ceases. The intensity of this movement depends also on the absolute temperature. Bacteria may flocculate spontaneously if the viscosity of the medium is increased to a certain degree. In this relation different micro-organisms show different sensitiveness, which seems to depend on the dimension of the bacterial surface. Mediums of higher viscosity hinder the bacterial agglutination caused by immune serum; this is an effect on the first phase of the immune agglutination, i. e., on the process of adsorption of the immune bodies.

AUTHOR'S SUMMARY.

IMMUNOLOGIC STUDIES IN BLASTOMYCOSIS. ANNA DEAN DULANEY, J. Immunol. **19**:357, 1930.

In the usual course of infection with *Blastomyces dermatitidis* antibodies do not seem to be formed to any appreciable degree. The production of antibodies may be stimulated by the use of an autogenous vaccine. In the case of one patient, marked improvement followed the use of the vaccine. The highest titer of complement-fixing antibodies was demonstrated at the time when the patient showed the most marked clinical improvement. With progress of the disease, the antibody titer decreased. Antibodies, chiefly complement-fixing substances, may be experimentally produced in rabbits on injection of the *Blastomyces* antigens. The mycelial, oidial and yeast forms of the same strain of *Blastomyces* stimulate identical antibodies. No species-specificity could be demonstrated in *Blastomyces*. Slightly positive results were obtained with closely related yeasts. Specific results were obtained on titration of the serums.

AUTHOR'S SUMMARY.

ANTIGENIC ANALYSIS OF CULTURES OF *B. PARADYSENTERIAE* AND *B. MORGANI*. G. M. MACKENZIE and LOUISE N. BATT, J. Immunol. **19**:371, 1930.

*B. paradysesterae* and *B. morgani* were found in an outbreak of summer diarrhea. Normal agglutinins for the dysentery group were found in horse, rabbit and human serums. They were only present in horse serum for *B. morgani*. A study of agglutinins in the serums of patients failed to give evidence that these two organisms were the cause of the infection. Cross-agglutination and absorption tests with immune serums showed the five strains of *B. paradysesterae* to be the same. In this manner four cultures of *B. morgani* were shown to represent three different strains. The *B. paradysesterae* isolated during the epidemic contained an antigenic component which was present in one culture of *B. morgani*.

EDNA DELVES.

BACTERIAL PRECIPITIN REACTION AND THE RAMON FLOCCULATION. ELIZABETH LEE HAZEN, J. Immunol. **19**:393, 1930.

Flocculation in mixtures of filtrate of *C. diphtheriae* and antitoxin is not limited by agglutination types (2,11) of the organisms which serve for the production of toxin. Precipitation in mixtures of toxic filtrate and agglutinating serum is restricted to agglutination types. Removal of the nontoxic precipitinogens from the toxic filtrate after contact with a specific precipitating serum has little, if any, effect on the Li of the toxin, but prevents subsequent precipitation of the filtrate with the homologous precipitating serum. The property in the toxic filtrate essential for flocculation with antitoxin is destroyed at a temperature of 60 C. for one-half hour, whereas the property essential for precipitation of agglutinating serum is not destroyed at a temperature of 85 C. for one hour. Removal of the bacterial antibody from antitoxic serum by adsorption of the serum with bacterial extracts does not prevent subsequent flocculation of the serum with the toxic filtrate, whereas the agglutinating serum treated in the same manner no longer precipitates with the toxic filtrate. The Ramon reaction is probably due to interaction between toxin and antitoxin and not between bacterial precipitinogen and precipitin.

AUTHOR'S SUMMARY.

ON THE DIALYZABILITY OF PROTEINS. ARTHUR F. COCA, J. Immunol. **19**:405, 1930.

The dialyzability of the excitants of atopic hypersensitiveness in egg white reported by W. Jadassohn is confirmed. With the aid of specific antisera and chemical methods the dialyzable excitants are shown to be native proteins. The proteins in the dialysate are antigens.

AUTHOR'S SUMMARY.

THE TRANSFER OF THE SKIN-REACTING ANTIBODY IN HUMAN SERUM TO GUINEA PIG SKIN. SUSAN GRIFFITH RAMSDELL, J. Immunol. **19**:411, 1930.

A specific reaction in the skin of the guinea-pig may be obtained, with fair regularity, when the test antigen can be used in a considerable concentration, on transfer of the serum of asthmatic subjects to the skin of the animal. The serums of patients with hay-fever, urticaria and eczema only occasionally transfer this reaction. This failure is ascribed to a relatively low antibody content in such serums and to the limitations of the technic used.

AUTHOR'S SUMMARY.

THE EFFECT OF NORMAL SERUM ON ANTIPNEUMOCOCCUS SERUM, TYPE 1. O. H. ROBERTSON, RICHARD H. P. SIA and M. AGNES CORNWELL, J. Immunol. **19**:429, 1930.

With a view to obtaining a clearer understanding of the environmental conditions under which pneumococcus immune serum exerts its optimum antibacterial action, a study was made of the influence of fresh normal serum on the

pneumococcal-promoting action of antipneumococcus serum type 1 in normal rabbit serum-leukocyte mixtures. It was found that the substitution of inactivated normal adult rabbit serum for fresh serum largely deprived the immune serum of its power to confer pneumococcus-destroying properties on the serum-leukocyte mixtures. In the absence of fresh serum, relatively high concentrations of immune serum had to be employed to produce a demonstrable killing effect. However, if instead of adult rabbit serum inactivated serum of young rabbits was used, the pneumococcal-promoting action of the immune serum was completely abolished. This could be restored by the addition of relatively small quantities of fresh serum to the inactivated serum-leukocyte mixture. Furthermore, there was found to be a constant quantitative relationship between the effective dilution of immune serum and the amount of fresh serum necessary; the higher the dilution of immune serum the greater was the quantity of fresh serum required to make it effective. It was shown that the interaction of pneumococcus antigen and antibody in the normal serum deprived it of activating properties. Observations were then made to determine whether or not a similar diminution occurs in the body during the course of pneumococcus infection. Tests on the serum of experimentally infected animals and from cases of lobar pneumonia in man showed no notable impairment of its activating function.

## AUTHORS' SUMMARY.

THE COMPARATIVE VALUE OF ROUGH AND SMOOTH STRAINS OF *B. TYPHOSUS* IN TYPHOID VACCINES. FRANCIS B. GRINNELL, J. Immunol. **19**:457, 1930.

The customary course of prophylaxis with a vaccine made from a rough strain of *B. typhosus* "Rawlins" produces little or no increase in the bactericidal power of the blood. A similar course of treatment with a vaccine made from a smooth, virulent strain of *B. typhosus* causes a considerable increase in the bactericidal antibodies. So far as the bactericidal test is an index of the resistance of the patient, typhoid vaccine in which rough strains of the organism are employed are valueless for prophylaxis. Vaccination with rough strains leads to the production of agglutinins for the virulent strains with no increase in the bactericidal power of the blood. Agglutination is therefore not an adequate test of the resistance of the person.

## AUTHOR'S SUMMARY.

ON THE HEAT STABILITY OF THE DIPHTHERIA TOXIN. K. ANDO and H. NISHIMURA, J. Immunol. **19**:465, 1930.

The heat sensitiveness of the diphtheria toxin depends on its own  $p_H$  under which it is heated. The more acidified the toxin, the more heat-stable it is. Diphtheria toxin is practically destroyed by heating it to 80 or 90 C. for thirty minutes, but not completely even by boiling for thirty minutes. When it was acidified to a  $p_H$  of 2 prior to boiling, about  $\frac{1}{1000}$  to  $\frac{1}{700}$  of its original toxicity remained after boiling for thirty minutes. Accordingly, the property of heat sensitiveness accepted hitherto as such must not be considered as a general characteristic of bacterial exotoxins.

## AUTHORS' SUMMARY.

CONCENTRATION OF ANTIPNEUMOCOCCIC AND ANTIMENINGOCOCCIC SERUMS. KENNETH GOODNER, J. Immunol. **19**:473, 1930.

In the course of immunization of horses against the meningococcus and the pneumococcus there is generally an increase in the serum of euglobulin of low solubility. The antibody of the immune serum is associated with this protein. Certain of the solubility characters of this antibody euglobulin are reported, and it is shown that in most instances it is unnecessary to concentrate this protein as a whole, for the greater part of the antibody is associated with the least soluble fraction of this protein. A method, based on these studies, is given for the routine concentration of antipneumococcic and antimeningococcic horse serums.

## AUTHOR'S SUMMARY.

THE QUANTITATIVE RESPONSE OF INTESTINE FROM SENSITIZED GUINEA-PIGS TO HOMOLOGOUS PROTEIN AND TO HISTAMINE. A. I. KENDALL and F. O. SHUMATE, J. Infect. Dis. 47:267, 1930.

A quantitative estimation of the degree of sensitization induced in guinea-pigs was reached by a determination of the minimal amount of homologous protein required to induce a maximal contracture in a series of strips of intestine taken from the sensitized animal. In making these tests, it is essential to use the ileal section of the gut; the duodenal end is distinctly less reactive both to contact with the homologous protein and to histamine.

AUTHORS' SUMMARY.

THE ANAPHYLACTIC REACTION IN SMOOTH MUSCLE. A. I. KENDALL, J. Infect. Dis. 47:284, 1930.

A strip of isolated, surviving intestine from a highly sensitized guinea-pig may be thrown into a series of maximal contractures by alternately exposing the strips to diluted antigen and to fresh Tyrode solution. The contraction induced by the former is "washed out" in the latter. A time comes when the strip will no longer respond to even high concentrations of the antigen. This is construed as evidence of a desensitization. It will, however, still contract in characteristic manner in contact with a threshold stimulating dose of histamine. Desensitization, therefore, is regarded as a gradual exhaustion of a specific, "sessile" antibody resident in the smooth muscle of the intestine of the guinea-pig. The fact that after exhaustion of this hypothetical specific antibody, the smooth muscle will still shorten in response to a smooth muscle contractant, is regarded both as evidence of the quantitative character of the reaction and as an indication that the antibody is actually within the smooth muscle tissue, from which it cannot be removed readily by washing with physiologic solutions, but in which it may be exhausted by contact with the specific antigen. The bearing of these observations on the "histamine" theory of anaphylaxis is discussed.

AUTHOR'S SUMMARY.

EXPERIMENTS WITH CERTAIN REACTIVE FACTORS OF ASCARIS. HAMILTON R. FISHBACK, J. Infect. Dis. 47:345, 1930.

Extracts of *Ascaris* in different solvents were found to possess a strong but variable hemolytic action on human red blood cells suspended in saline solution. Small doses of serum from young rabbits immunized against *Ascaris* substance completely inhibited hemolysis by the *Ascaris* extracts. Uterine strips from sensitized guinea-pigs responded specifically to the *Ascaris* extracts. After incubation with immune serum, the acetone-insoluble, alcohol-soluble extracts caused no excitation of the uterine strip, while the saline solution extract was still active. The exciting factor remaining in the latter extract was its protein content. In an allergic human subject, the results of intradermal tests with *Ascaris* extracts were positive. Here, also, the reactivity of the acetone-insoluble, alcohol-soluble extract was neutralized by immune serum, while that of the saline solution extract was not diminished. The immune content of the serum thus was specific against the toxin-producing hemolysis of red blood cells and against the oxytotic and skin reactive factors of the acetone-insoluble, alcohol-soluble *Ascaris* extract, but was ineffective against the saline solution extract.

AUTHOR'S SUMMARY.

THE NEUTRALIZATION OF THE VIRUS OF POLIOMYELITIS BY HUMAN SERUM. H. J. SHAUGHNESSY, P. H. HARMON and F. B. GORDON, J. Prev. Med. 4:463, 1930.

Human serums mixed, in various dilutions, with the virus of poliomyelitis were inoculated intracerebrally into monkeys of the genus *Macacus rhesus*. Serums from ten normal adults and six normal city children neutralized the virus in final

dilutions as high as 1:30, in a large majority of the tests. Serums from three of four rural children and four of five normal infants showed practically no neutralizing power. Serums from fourteen convalescents from poliomyelitis, even those recovered within two years, showed less neutralizing power than the serums of normal adults and normal city children. Serums from seven familial contacts of patients with poliomyelitis showed about the same neutralizing power as serums from normal adults. It is possible that immunity against poliomyelitis develops in a way similar to immunity against diphtheria. Tested normal serums may prove as effective as convalescent serum in the treatment of poliomyelitis.

## AUTHORS' SUMMARY.

ISOHAEMAGGLUTININS IN PREGNANCY. KATHLEEN EDGEcombe, J. Path. & Bact. **33**:963, 1930.

The bloods of eighteen women have been tested at various periods of pregnancy, from fifteen to forty weeks, and the bloods from their babies examined at birth. The fetus had a definite influence on the titer of the mother's blood as follows: With a fetus of no group at birth, the mother's blood showed little or no change during pregnancy; with a fetus of the same group, the mother's blood showed an increase of titer (cells + 16 per cent, serum + 86 per cent); with a fetus of a different group, the mother's blood showed a much greater rise in titer (cells + 83 per cent, serum + 330 per cent). Three bloods were tested from five to nine months after pregnancy. One that had shown no increase during pregnancy showed little alteration, and two in which there had been an increase during pregnancy showed a fall practically to the original level.

## AUTHOR'S SUMMARY.

ANAPHYLACTIC RESPONSES OF THE GUINEA-PIG'S SKIN. C. E. KELLETT, J. Path. & Bact. **33**:981, 1930.

The response of the guinea-pig's skin to simple forms of trauma, to histamine and to trauma occasioned by local antibody-antigen reaction differs from that of man in that the arteriolar flare is rudimentary and barely detectable. The local response of the guinea-pig's skin to local reaction of antigen and antibody has been described under three main types which grade one into the other, and which seem to be, in the main, dependent on the local concentration of antibody. A generalized response of the skin occurs if the antigen is suitably introduced into a passively or actively sensitized guinea-pig. A similar response on or about the sixth day may follow on a single massive dose of antigen. After a dose of horse serum, guinea-pigs will die of acute anaphylactic shock on the introduction of anti-horse rabbit serum if an incubation period of at least three fourths of an hour is allowed.

## AUTHOR'S SUMMARY.

INTRADERMAL TESTS WITH EXTRACT OF LEPROUS SKIN. S. LYLE CUMMINS and J. J. DU PRÉ LE ROUX, *Tubercle* **11**:299, 1930.

Lepers and nonlepers were tested with various dilutions of an extract in physiologic solution of sodium chloride of a piece of leprous skin rich in Hansen's bacillus, the extract being sterilized by autoclaving for an hour. There was a lower response of the nonleprous groups to the extract as compared with that of lepers, and this is considered evidence against the probability of a latent factor of leprosy playing any considerable part in the high reactivity of "healthy" natives tested in South Africa. A tuberculous group gave no sign of being more reactive than a nontuberculous group of nonlepers.

## H. J. CORPER.

SEROLOGIC RELATIONS OF YEASTLIKE FUNGI. C. E. LIM and T. J. KURUTCH-KIN, *Nat. M. J., China* **16**:338, 1930.

In studying the serologic relations of yeastlike fungi the use of water-soluble substances in the fungi as antigens has been found to give good results.

HEALING OF NECROTIC LESIONS PRODUCED BY BCG VACCINE. J. ZEYLAND, *Ann. de l'Inst. Pasteur* **45**:157, 1930.

Necrotic lesions produced by BCG vaccine in heavy doses in animals have been noted by several authors. With such heavy masses, killed organisms will, of course, produce identical tubercles, with necrosis. A series of twenty-three rabbits was observed following injection of BCG directly into the kidney, for periods to twenty-six months. There appeared, first, necrosis around the wound, enclosing great masses of BCG, surrounded by polymorphonuclears, some phagocytic. In two weeks, a great necrotic area was surrounded by typical tuberculous tissue, well vascularized. In the second month, calcified areas appeared in the necrotic mass, and the surrounding tissue lost its specific appearance. After a year, various stages of healing obtained. The organisms were rare; the lesions, small. Finally, healing appeared virtually complete, with minor scar tissue. The benignity of the vaccine, even under these extreme conditions, seems assured.

M. S. MARSHALL.

DIPHTHERIA IMMUNIZATION WITH ANATOXIN. G. RAMON, *Ann. de l'Inst. Pasteur* **45**:291, 1930.

In an article reviewing the history of his diphtheria anatoxin since its first use in 1923, Ramon affirms that this product has been adequately demonstrated to be innocuous (at the time of writing over 7,000 liters had been distributed under his supervision). Its value parallels a function of the flocculating property with antitoxin. It will, properly used, immunize 94 to 98 per cent of those treated, as demonstrated by the Schick test. Immunized persons are demonstrably immune for over four years and probably much longer or for life. It may be injected with a sterile protein (as typhoid vaccine) to confer a superior immunity of long duration. Immunity is rapidly developed. The proper doses are 0.5 cc., 1 cc. and 1.5 cc., given subcutaneously at intervals of three weeks and of fifteen days, respectively.

M. S. MARSHALL.

THE ANTITOXIN CONTENT IN SERUM FOLLOWING IMMUNIZATION WITH DIPHTHERIA ANATOXIN. G. RAMON and ROBERT DEBRÉ, *Ann. de l'Inst. Pasteur* **45**:326, 1930.

A negative reaction to the Schick test, indicating at least 0.033 Ehrlich unit of diphtheria antitoxin per cubic centimeter of serum, is insufficient to determine the antitoxin following immunization with anatoxin. Of one series of 105 children, the authors found 40.9 per cent showing over one unit per cubic centimeter, 49.2 per cent over 0.1 unit, 5.7 per cent over 0.033 unit and 3.8 per cent less than 0.033 unit. Either two or three injections seemed to vary these results relatively little. Figures indicate more antitoxin in older immunized children than in infants, but the evidence is based on few cases. Perhaps the most interesting group considered is a series, part of which was immunized in 1925, part in 1926, part in 1927 and part in 1928. The antitoxin content varied from over 1 unit per cubic centimeter (44 per cent of the four year group) down. The percentages are not statistically significant, but a good immunity seems assured in most cases, and one of great stability for some years, at least.

M. S. MARSHALL.

THE CONSTITUTION OF TOXIN AND ANTITOXIN AND THEIR MODE OF UNION. S. SCHMIDT, *Ann. de l'Inst. Pasteur* **45**:337, 1930.

The theories of physical or chemical union of toxin and antitoxin are discussed at length, following the school of Arrhenius and Madsen, particularly relative to the Ramon flocculation reaction. Essentially a review of some of the work during recent years, matters of rapidity, stability, reversibility, and avidity in flocculation are considered relative to their theoretical interpretation. No new work is presented, and no conclusions are drawn.

M. S. MARSHALL.

ATTEMPTS TO INFLUENCE SPONTANEOUS TUBERCULOSIS IN RHESUS MACACUS BY PERORAL ADMINISTRATION OF BCG. A. NOHLEN, Beitr. z. Klin. d. Tuberk. **74**:532, 1930.

Seven monkeys each received perorally 5 mg. of virulent human tubercle bacilli twice at an interval of forty-eight hours. In all the animals progressive tuberculosis developed, which in six of them produced definitely open foci. Seven other animals each received perorally, three times, 0.05 Gm. of Calmette-Guérin bacilli. Thirty-three days later these animals were brought in contact with seven normal controls and with the seven infected animals. In five of these experiments the vaccinated animals showed no protective action of BCG, with the exception of a slight increase in their survival time. In one experiment both the normal control and the vaccinated animal remained healthy; in one experiment tuberculosis developed in the control, while the vaccinated animal remained healthy. The vaccination with BCG produced no untoward results.

MAX PINNER.

TUBERCULOUS REINFECTION AND ITS RELATION TO ALLERGY AND IMMUNITY. E. A. SCHNIEDER, Beitr. z. Klin. d. Tuberk. **74**:583, 1930.

The bearers of healed tuberculous foci remain allergic for a certain period following the healing.

MAX PINNER.

FORMATION OF AGGLUTININ ON INTRACUTANEOUS INJECTION OF PARATYPHOID B. J. SZÉP, Ztschr. f. Immunitätsforsch. u. exper. Therap. **68**:274, 1930.

The intracutaneous injection of emulsion of *B. paratyphosus* B causes in rabbits much greater production of agglutinin than the subcutaneous injection of the same amount of the emulsion.

TITERS OF ISO-AGGLUTININS IN TUBERCULOSIS. H. ZANTOP, Ztschr. f. Immunitätsforsch. u. exper. Therap. **68**:277, 1930.

On careful comparison of available results there appears to be no noteworthy change in the titers of the iso-agglutinins in tuberculous patients.

IMMUNITY AGAINST PYOGENIC ORGANISMS. ALFRED PETTERSON, Ztschr. f. Immunitätsforsch. u. exper. Therap. **68**:304, 1930.

The antibacterial agency providing resistance against pyogenic infections with *Staphylococcus* and *Bacillus pyogenes* is not the bactericidal substances of the fluids of the body, but the polymorphonuclear leukocytes.

AMINES AS ANTIGENS. Z. JERMOLJEW and I. BUJANOUSKAJA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **68**:342, 1930.

A series of amines (trimethylamine, heptylamine, heptodezylamine) gave precipitation and fixation with homologous antisera.

THE ORIGIN OF COMPLEMENT. E. FRIEDBERGER and J. GURWITZ, Ztschr. f. Immunitätsforsch. u. exper. Therap. **68**:351, 1930.

In the course of a study of the immune properties of normal serum it was found that complement is present in the serum of newly born guinea-pigs to about the same extent as in the mother. The complement makes its appearance in the serum in the very last stages of fetal life.

EFFECT OF BCG VACCINATION OF NEW-BORN GUINEA-PIGS BY MOUTH. A. I. TOGUNOWA and M. M. LARIONOWA, *Ztschr. f. Tuberk.* **57**:312, 1930.

Within the first few days after birth guinea-pigs received from 3.75 to 15 mg. of Calmette-Guérin bacilli by mouth. They developed normally. After from one to two months about half of the animals had a temporary weak tuberculin allergy. Calmette-Guérin bacilli were demonstrable in the cervical and mesenteric lymph nodes and in the liver, and they were resorbed within the first few days after the administration. None of the animals showed lesions of progressive tuberculosis. The vaccinated animals had no definitely demonstrable immunity to a definitely virulent reinfection.

MAX PINNER.

REACTION IN EXPERIMENTAL TUBERCULOUS REINFECTION. E. A. SCHNIEDER, *Ztschr. f. Tuberk.* **58**:33, 1930.

Rabbits were infected in the cornea with Calmette-Guérin bacilli and reinfected with minimal amounts of virulent bovine bacilli from 280 to 290 days after the first infection. The reinfected tissue was expelled in toto, leaving a round clean cavity in the cornea. The author believes that this phenomenon is essentially the same as that which leads to the formation of the round early cavities following an early infiltration.

MAX PINNER.

THE EOSINOPHIL LEUKOCYTES IN IMMUNIZATION OF HORSES WITH DIPHTHERIA TOXIN. I. FREUCHEN, *Acta path. et microbiol. Scandinav. (supp. 3)*, p. 123, 1930.

The number of eosinophil leukocytes falls off as diphtheria toxin is injected and as the antitoxin in the blood increases in amount. As the antitoxin decreases, the number of eosinophils increases. The variations in the number of eosinophils are greater than the variations in the numbers of all the leukocytes and go in a contrary direction. The course of the eosinophils is similar to that in the majority of infectious diseases.

### Tumors

EFFECT OF DYES ON THE VIRUS OF CHICKEN TUMOR NO. 1. MARGARET REED LEWIS, *Am. J. Hyg.* **12**:288, 1930.

The causative agent of the chicken tumor no. 1 may be inactivated in the tumor extract by a number of the common biologic dyes. Some of these dyes brought about an unfavorable hydrogen-ion concentration in the solution containing the virus. Of those that did not produce an unfavorable hydrogen-ion concentration, toluidin blue, eosin, erythrosin, phenol indophenol, and dichlorophenol indophenol exhibited great inactivating power on the virus. Toluidin blue inactivated the virus of the chicken sarcoma in solutions containing about one part of dye to 10,000 parts of a highly virulent tumor extract.

AUTHOR'S SUMMARY.

CARCINOMA OF THE FEMALE GENITAL TRACT IN CHILDHOOD. A. H. MORSE, *Am. J. Obst. & Gynec.* **19**:520, 1930.

The literature contains a single record each of carcinoma of the vulva and carcinoma of the vagina, and eight records of a growth involving the uterus, in early childhood. A case is reported of a child, 10 years of age, who for two years had had a vaginal discharge followed by bleeding. Necrotic bits of tissue passed during an examination proved to come from an inoperable adenocarcinoma of the cervix.

A. J. KOBAK.

HEMANGIOMA OF THE PELVIC CONNECTIVE TISSUE. ROBERT T. FRANK, Am. J. Obst. & Gynec. **20**:81, 1930.

In an unmarried woman, 35 years old, a pelvic mass that reached the level of the navel on the right side and appeared to be continuous with the uterus was removed with great difficulty. It was vascular, cystic and edematous, and had many adhesions. The tissue was a simple hemangioma the septums of which consisted of loose, edematous, fibrillar connective tissue. The origin of the structure, which showed no intimate relationship with either uterus, adnexa, intestines or bladder, was apparently from the pelvic connective tissue. Six years previously a similar tumor had been removed from the left broad ligament. Two years after the second removal there was a third recurrence, which seemed to be arrested by radium. The author failed to find in the literature any report of a similar hemangioma of the pelvic connective tissue.

A. J. KOBAK.

CHORIOEPITHELIOMA, WITH SPECIAL REFERENCE TO DISAPPEARANCE OF THE PRIMARY UTERINE TUMOR. EMIL NOVAK and A. K. KOFF, Am. J. Obst. & Gynec. **20**:153, 1930.

The authors classify trophoblastic tumors as benign or malignant choriomas; the former include the benign hydatidiform mole, and the latter take up Ewing's group of chorio-epitheliomas. A report is made of a white woman, 35 years old, in whom, following a curettage for "retained tissue following abortion," metastatic growths developed in the lungs and brain, which proved to be chorio-epithelioma, while the uterus failed to show any primary tumor. Further study of the slide with the original curettings showed syncytium and Langhan's cells with definite malignant characteristics, such as mitosis and hyperchromatosis. Other cases of this type recorded in the literature are cited, and the explanations offered for the disappearance of the uterine tumor are reviewed.

A. J. KOBAK.

TUBERCULOSIS AND CANCER. W. C. HUEPER, Am. Rev. Tuberc. **22**:271, 1930.

The doctrine of an antagonism between active tuberculosis and cancer is supported by numerous and reliable experimental and statistical data, and has by far more evidence in its favor than any other conception of this matter. No definite conclusions can be drawn from the material available concerning the causative mechanism of this phenomenon, because reliable and extensive investigations into the effect of primary constitutional, secondary reactive and secondary mechanical factors of tuberculosis on the malignant growth do not exist. A direct toxic effect of tubercle bacilli on the cancer cells appears to be improbable.

H. J. CORPER.

MULTIPLE GLIOMAS OF THE BRAIN. KIVOSHI HOSOI, Arch. Neurol. & Psychiat. **24**:311, 1930.

In Hosoi's patient, a man aged 44, two days following an automobile accident trouble with speech developed (he could not pronounce words well) which grew steadily worse. He also vomited repeatedly, became incontinent and unsteady on his feet, and a right-sided hemiplegia developed. A few months before the accident, the patient had queer feelings and fears that he might lose his mind, but otherwise he was never sick. Neurologic examination revealed paralysis of the lower branch of the right facial nerve, hypo-active tendon reflex, fair voluntary movements in the extremities, a Kernig and a bilateral Babinski sign. The ankle jerks were absent. The pupils reacted normally, and the fundi showed congested retinal veins. As a glioma was suspected, a subtemporal decompression was done. An inoperable subcortical tumor was located in the left motor area.

Necropsy, which was performed one-half hour after death revealed one hemorrhagic glioma under the rostrum of the corpus callosum involving the right more than the left hemisphere, a similar tumor over the left motor area extending into the corona radiata and a third, smaller tumor in the left putamen. Microscopically the gliomas were generally of the astrocytic variety, but in some places showed a more diversified structure. Hosoi considers the three tumors of independent, multicentric, not metastatic origin.

G. B. HASSIN.

GANGLIOGLIOMA. CYRIL B. COURVILLE, *Arch. Neurol. & Psychiat.* **24**:439, 1930.

Ganglioglioma is a tumor made up of ganglion and glia elements. In these tumors the cells are fairly advanced in their differentiation, the adult forms being rather conspicuous. After reviewing eighteen cases from the literature, Courville describes two cases of his own. In one, the tumor was in a girl, aged 15, and arose from the tuber cinereum. At the age of 4 the child became idiotic, blind, hydrocephalic, and completely paralyzed on both sides. After a cyst in the left parietal lobe was evacuated, the patient recovered "almost completely," but within a year the condition became worse again. Another operation, with the removal of the cyst, improved the child's mental condition, but blindness developed in the right eye, and the right side of the body became paralyzed. At the age of 15, after an injury, convulsions developed followed by death. Necropsy revealed a suprasellar tumor, 3.5 cm. long and about 1.5 cm. in diameter, and a cyst in the left hemisphere, 9 by 6 by 7 cm., which contained in its anteromedian aspect a small tumor which was continuous with the previous tumor mass. Both lateral ventricles were dilated; the structures of the basal ganglions were distorted, and in some instances was unrecognizable. Specific staining methods (Cajal, Schultze-Stöhr) showed neuroblasts without or with processes, well developed ganglion cells usually in a state of degeneration and nerve fibers which were all unmyelinated and often varicose. In addition there were spongioblasts, unipolar, bipolar and fully developed and astrocytes (in the wall of the cyst only). A reticular network of glia fibers could be demonstrated with the methods of Mallory and Alzheimer. Blood vessels were numerous; they were infiltrated with lymphocytic elements and represented the connective tissue of the tumor masses. Fat was present in the form of minute granules. The main components of the tumor were ganglion and glial cells—a ganglioglioma of the tuber cinereum—"the fifth case to be reported in this location."

In the second case, with no history, a tumor from 1 to 2 mm. in diameter was found in the tuber cinereum behind and to the left of the infundibulum. It was cellular; ganglion and glia cells and probably neuroblasts were embedded in a loose stroma; glia fibers were numerous and with the rich capillary network formed the larger part of the intercellular substance.

Of the numerous names given such tumors (ganglionic neuroma, neuro-ganglioma, neuroglioma, ganglioneuroma, ganglioglia-neuroma and ganglionic glioma) Courville prefers the term ganglioglioma because the tumors contain both ganglion cells and neuroglia. In the tuber cinereum this type of tumor most likely arises in the indifferent cells of the basal plate of the diencephalon.

G. B. HASSIN.

SYSTEMIC INFLUENCES IN IMMUNITY AND CANCER. ARTHUR EASTWOOD, *J. Hyg.* **30**:267, 1930.

The idea that there are systemic influences concerned with the genesis of cancer has assumed many forms and is often expressed ambiguously. Does it mean that normal cells have a "natural tendency" to malignant growth and actually become malignant if freed from systemic control? I do not accept this "natural tendency"; unrestrained growth does not suffice to explain the origin of cancer. What is meant by "systemic control"? My view is that such control regulates normal cells,

and that cancer cells are independent of it; I do not agree that there is a special kind of antimalignant systemic control that may destroy the fully fledged cancer cell. What is the nature of "susceptibility" to the change into the cancerous condition? I regard it as essentially a cellular property, not as a humoral or systemic influence, though I admit that irritant material that gains access to the circulation may increase the susceptibility of particular cells. What is meant by "resistance" (either local or systemic) to cancer? Owing to the recuperative powers of the animal body, local disturbances of metabolism are often corrected, and there is a return to the normal condition; some of these disturbances, if left uncorrected, might lead to cancer, and the fact that they are corrected may, if one likes, be called resistance to the genesis of cancer. It is also known that true cancerous foci or metastases may remain quiescent for a considerable time; but I do not agree that such quiescence has been shown to be attributable to a specific kind of antimalignant "resistance" (either local or systemic).

While there is no satisfactory evidence, either direct or indirect, of a systemic influence that causes cancer, systemic influences are so complex and obscure that this possibility cannot be definitely excluded. But there does not seem to be any cogent reason for dissenting from the view that the production of the malignant variant is due to its local environment.

AUTHOR'S SUMMARY.

EXTRACT OF ADRENAL CORTEX AND CANCER. S. ITAMI and E. McDONALD, *Science* **72**:460, 1930.

Spontaneous carcinoma of the breast in the mouse was treated by the extract of adrenal cortex of Swingle and Pfiffner, without any curative or restraining effect on the tumor. No therapeutic value in the treatment for such cancers in animals was shown in the cortical hormone, although the efficacy of this preparation in substituting for the adrenal cortex hormone in adrenalectomized animals has been thoroughly proved. The use of such extract of adrenal cortex in human patients is therefore not to be recommended as a treatment for cancer, but this in no way detracts from the value of this extract of adrenal cortex of Swingle and Pfiffner in conditions other than cancer, as it has been proved to be effective as a substitute for the cortical hormone.

AUTHORS' CONCLUSIONS.

TUMORS OF THE PAROTID GLAND. E. B. BENEDICT and J. V. MEIGS, Surg. Gynec. Obst. **51**:626, 1930.

Study of eighty cases of tumors of the parotid gland showed that a mixed tumor grows slowly, but occasionally increases in size rapidly because of superimposed sarcomatous or carcinomatous changes and commonly recurs after excision. Carcinoma was diagnosed in thirty of the patients; in whom metastases were present in the lungs, bones and skin. In nine sarcoma was diagnosed. In seven the gland was secondarily invaded by carcinoma, melanotic sarcoma and malignant lymphoma. Nothing new is added to the classification of Ewing.

RICHARD A. LIFVENDAHL.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBES. W. W. HOLLAND, Surg. Gynec. Obst. **51**:683, 1930.

Primary carcinoma of the fallopian tubes was found in 9 of 10,000 cases of completely removed tubes; in 70 cases the tubes were secondarily involved from carcinoma of the uterus or ovary. In 1 case bilateral carcinoma was associated with tuberculosis. From the examination of these tubes it appears that inflammatory changes do not deserve the etiologic significance in carcinoma attributed to them by many writers.

RICHARD A. LIFVENDAHL.

THE USE OF HEPARIN PLASMA FOR THE GRAFTING OF SPONTANEOUS MAMMALIAN TUMOURS INTO HOMOLOGOUS ANIMALS. M. J. A. DES LIGNERIS, *Brit. J. Exper. Path.* **11**:249, 1930.

In a case of melanoma in an Angora goat, grafting which had previously failed was successful when heparin-treated goat plasma was used as a nutritive and protective medium surrounding the transplanted particles of tumor.

AUTHOR'S SUMMARY.

VENOUS INVASION IN METASTATIC TUMORS IN THE LIVER. RUPERT A. WILLIS, *J. Path. & Bact.* **33**:849, 1930.

From a series of 120 consecutive autopsies in cases of malignant disease, 12 are selected to exemplify the importance of malignant penetration of the afferent and efferent veins of the liver in the metastatic spread of tumors to and from that viscus. Invasion of the larger tributary portal vessels or of the portal vein itself by neoplasms, primary or secondary, in the portal drainage area is a potent factor in producing widespread multiple hepatic metastases by portal embolism. Established hepatic growths, whether primary or metastatic, and of the latter whether sown in the liver by the portal or arterial blood, frequently penetrate adjacent branches of the portal system and produce corresponding regional broods of further metastases in the liver. These factors alone or combined are responsible for the familiar bulky liver thickly studded with secondary growths. Invasion of the efferent veins of the liver by intrahepatic growths is an important factor in further metastatic dissemination to the lungs. Penetration of the inferior vena cava itself may occur.

AUTHOR'S SUMMARY.

SACRAL CHORDOMA WITH WIDESPREAD METASTASES. RUPERT A. WILLIS, *J. Path. & Bact.* **33**:1035, 1930.

An unusual malignant sacral chordoma is recorded which presented the following features: the primary tumor was one of the largest, if not actually the largest, so far described; prolific remote metastases, probably due to tumor invasion of the iliac veins, were present in the lungs, the heart, the liver, the spleen, the kidneys, the thyroid gland and the skin; the patient also presented numerous exostoses of many bones; the possibility that these and the chordal tumor may both be expressions of a constitutional tendency to skeletal anomalies is discussed.

AUTHOR'S SUMMARY.

A PULMONARY NEOPLASM SIMULATING TUBERCULOSIS IN ADOLESCENCE. D. P. SUTHERLAND and J. R. BEAL, *Tubercle* **11**:529, 1930.

An interesting case of primary carcinoma of the lung in a patient 17 years of age is reported—an extremely rare condition. The atypical symptoms to which the growth gave rise, and more especially an obstruction of the common bile duct due to a pancreatic stoppage, are regarded as unusual in carcinoma of the lung. The history, clinical examination and roentgen appearances pointed to pulmonary tuberculosis. Only when signs of pressure, such as obstruction to the biliary passages, began to appear did the diagnosis of neoplasm of the lung suggest itself.

H. J. CORPER.

THE MICROSCOPIC STRUCTURE OF GIANT CELL EPULIS. I. WALLGREN, *Arb. a. d. path. Inst. zu Helsingfors* **6**:21, 1930.

Extensive studies are reported on the various elements comprising a giant cell epulis. The small cells which make up the bulk of this tumor are connected with one another by cell processes, and apparently are the predecessors of giant cells, although the origin of these giant cells from the endothelium of blood vessels is

admitted. Subcutaneous bone transplants in guinea-pigs were used to corroborate observations on numerous tumors. The results of the studies seem to justify the assumption that epulis is not granulation tissue, but a presarcomatous mass. Cell measurements, especially on nuclei and nucleoli, form the basis for the majority of the opinions expressed.

GEORGE RUKSTINAT.

THE CELL STRUCTURE OF EPITHELIAL TUMORS OF THE MAMMARY GLAND.  
A. KLOSSNER, Arb. a. d. path. Inst. zu Helsingfors 6:81, 1930.

In order to eliminate any possible confusion, the breast was studied in various phases of menstruation; no characteristic alterations in the cells were observed. It was found that in benign tumors, such as adenomas and fibro-adenomas, the cell structure remained normal, but in carcinoma the cells were definitely altered. The alterations were especially evident in the nuclei and the centrosomes. Also, in cancer cells, three or four centrioles occurred instead of the normal two.

GEORGE RUKSTINAT.

SALIVARY STONE WITH FORMATION OF CARCINOMA AT THE BASE OF THE TONGUE. R. BAYER, Centralbl. f. allg. Path. u. path. Anat. 49:102, 1930.

Embedded in a squamous cell carcinoma of the right side of the tongue, a salivary calculus, the size of a hazel nut, was found. There were metastases of the carcinoma to the regional lymph glands. When found in the midline, such stones usually arise in remnants of the thyroglossal duct. Bayer thinks the lateral position of the stone in his patient indicates an origin in one of the small salivary glands.

GEORGE RUKSTINAT.

MALIGNANT MELANOTIC TUMORS OF THE NAIL BED ON A TRAUMATIC BASIS.  
W. SCHOPPER, Centralbl. f. allg. Path. u. path. Anat. 49:195, 1930.

Malignant melanotic tumor of the thumb nail bed after trauma in two men is reported. In each instance the tumor developed about a year after the trauma, and was situated in tissue which was the site of chronic inflammation. In one instance the tumor metastasized to the axillary lymph glands. Evidence of preceding pigmented nevi, the usual source of such tumors, was lacking.

GEORGE RUKSTINAT.

ADENOMA OF THE PARATHYROID. M. ZAJEWLOSCHIN, Frankfurt. Ztschr. f. Path. 40:132, 1930.

After a short review of the literature, the author describes a tumor of the right parathyroid gland in a man 57 years old. The tumor was well separated from the thyroid gland. It measured 1.3 by 3 by 4.3 cm., and was of firm consistency. One portion showed a small cyst filled with clear liquid. Histologically, the tumor consisted of epithelial cells showing a netlike arrangement similar to that in the normal parathyroid gland. The cells varied in shape and size. In some portions, small lobules consisting of similar cells were recognizable. In other portions, small bands of connective tissue surrounded by groups of cells in palisade-like arrangement could be demonstrated by the van Gieson stain. Some of the cells showed their membranes very indistinctly, giving the impression of syncytial masses. Neither colloid nor follicles nor oxyphil cells were demonstrable. The author is of the opinion that the tumor was an actual new growth, rather than evidence of hyperplasia of the parathyroid gland.

O. SAPHIR.

MULTIPLE LEIOMYOMA SARCOMATODES OF THE STOMACH. A. ANTONOW, Frankfurt. Ztschr. f. Path. 40:173, 1930.

In a 21 year old woman who complained of gastric distress, multiple tumor nodules were found in the stomach during operation. The stomach, a few enlarged lymph nodes of the omentum and the gastrocolic ligament were resected. The

tumor nodules were found throughout the different layers of the stomach. Neither the serous surface nor the mucosa in the region of the nodules showed interruption of their continuity. Some of the nodules showed a few cysts, the walls of which were formed by broken-down tumor tissue. Histologically, the tumor consisted of immature muscle elements. Many cells were markedly vacuolated, their nuclei pushed over toward the peripheries of the cells. Some portions showed cells with oval or round nuclei and a hardly recognizable cytoplasm. Other sections contained many oval cells arranged in groups. Some of these groups were separated from one another by masses of erythrocytes located close to blood vessels. In other portions, oblong and spindle-shaped cells were present, many of which showed rounded edges. These cells were arranged in bundles extending in various directions. An invasion by many tumor cells into surrounding structures was noted. Many vascular slits were found. The lymph nodes showed an invasion by similar tumor cells. By the use of the Foot and Menard stain for reticulum, many reticulum fibers were demonstrated throughout the tumor. The author believes that the occurrence of multiple tumor nodules throughout the stomach in this case tends to support Conheim's and Fischer-Wasel's theories as to the origin of tumors.

O. SAPHIR.

PRECURSORY CHANGES TO CANCER IN THE ESOPHAGUS. H. SCHAEER, *Ztschr. f. Krebsforsch.* **31**:217, 1930.

Systematic studies were made of the esophagus of 237 persons over 40 years of age. Leukoplakia was found with some frequency in 67 per cent of the cases, and does not appear to play the important rôle in the development of cancer in the esophagus that it does in the development of cancer in the mouth. Varying degrees of chronic esophagitis were found with about the same frequency, but no parallelism could be found between this and epithelial hyperplasia. Traction diverticula were found in 12 patients, more frequently in men, as was the case with leukoplakia. These were often associated with epithelial overgrowths, and Schaeer regards them as playing an important part in the causation of cancer. In one patient an atypical epithelial growth was also observed in a small ulceration of the mucosa, either an unhealed peptic ulcer of the esophagus or an ulcerated diverticulum.

H. E. EGGERS.

FIVE HUNDRED CASES OF GASTRIC CANCER. T. POSCHARISKY, *Ztschr. f. Krebsforsch.* **31**:263, 1930.

A study of the autopsy protocols of 500 cases of gastric cancer is reported, with the following conclusions: Malignancy expressed in terms of dissemination is in part the function of age, in that metastasis is more frequent at earlier ages; in part, the morphologic character of the tumor, the more atypical ones showing the most constant tendency toward dissemination, and in part, the location of the primary tumor, since metastasis is more frequently lacking in carcinomas of the pylorus and increasingly frequent in the case of those of the cardia, fundus and pyloric antrum.

H. E. EGGERS.

THE SYMPTOMATOLOGY OF PRIMARY BRONCHIAL CANCER. C. KÜHN, *Ztschr. f. Krebsforsch.* **31**:276, 1930.

At the city hospital of New Cologne it was found in autopsies performed in all cases of cancer that in the five year periods since 1900 there has been an increase in the incidence of primary bronchial carcinoma, from 4.68 to 10.63 per cent. It was more frequent in men than in women, the ratio being 5:0.59, and occurred most often in the sixth and seventh decades of life. The usual primary sites were the right lung and the upper lobes of the lungs. An exudative pleuritis was present in 18 per cent of the cases, the exudate showing a predominance of

lymphocytes with some polymorphonuclears. Metastases were most usual in the liver, regional lymph glands, kidneys, bones, suprarenal glands and pleura and in the lung itself. No relationship was evident to tuberculosis, occupation or the specific irritative element.

H. E. EGGERS.

MULTIPLE PRIMARY CARCINOMAS AND THEIR FREQUENCY. R. F. MÜLLER, *Ztschr. f. Krebsforsch.* **31**:339, 1930.

Among the 1,121 cases of cancer coming to autopsy at the Allgemeinen Krankenhaus St. Georg at Hamburg during the last four years, there were 21 cases of multiple primary carcinoma. Basing his calculations on the incidence of cancer in proportion to the cause of other deaths at that institution, Müller estimates the theoretical incidence of such cases as 18—a close approximation to that actually observed, and indicating both a lack of atreptic immunity and of special predisposition. Among the curiosities of this series, there were observed an instance of the metastasis of one carcinoma, an epithelioma of the tongue; in another, a carcinoma of the lung; and a colliding growth of a carcinoma of the lung with an esophageal carcinoma.

H. E. EGGERS.

TESTICULAR TUBULAR ADENOMA OF OVARY. O. BERNER, *Norsk mag. f. lægevidensk.* **91**:1177, 1930.

In a woman, aged 22, with increasing symptoms and signs of hermaphroditism a round, firm, whitish tumor, almost the size of a fist, was found in the right ovary. The tumor, covered by a capsule of connective tissue, was doughlike, and its surface smooth, except in the region of the hilus. Cross-section showed a peculiar yellow color. The tumor consisted of numerous sharply defined lobes, separated by connective tissue containing fairly many and large blood vessels. In most of the lobes were numerous tubules, sometimes with compact masses of epithelium. In the intertubular connective tissue were large protoplasmic cells, each with a large bladder-shaped nucleus and distinct nucleoli. These cells, strongly resembling Leydig's cells of the testicle, contained fat in sudan-stained sections. Ovarian tissue was present in the capsule, especially in the thicker portion, which rested almost like a hood over the testicular part of the tumor. Four weeks after the operation normal menstruation occurred, and a gradual disappearance of hirsutism followed. A half year later nothing abnormal in the patient's body was observed apart from some enlargement of the clitoris. Berner states that, with Popoff's case (*ARCH. PATH.* **9**:31, 1930), this is the sixth case of testicular tubular adenoma of the ovary in the literature. It shows a remarkable similarity to the cases of Pick, Schickele, Neumann and Strassmann. The article is accompanied by photographs and a drawing in color.

### Medicolegal Pathology

GAS BACILLUS INFECTION OF THE BRAIN DEVELOPING THIRTEEN YEARS AFTER GUNSHOT INJURY. H. DÜRCK, *Beitr. z. path. Anat. u. z. allg. Path.* **84**: 667, 1930.

Dürck reports a case that he interprets as one of unusual latency of infection with the gas bacillus. The patient was a 34 year old criminal who was transferred from prison to the hospital in extremis. Eight days previously he had begun to feel ill, and two days before death he had what was described as a stroke of apoplexy. On his admission to the hospital the left side of his body was paralyzed. At necropsy there was found an abscess of the right cerebral hemisphere. The abscess contained gas and Welch-Fraenkel bacilli. In 1916, while in the army, the man had sustained a severe gunshot injury of the right side of the head. Dürck believes that the infecting organisms were introduced into the brain at this time and lay dormant until activated by some unknown cause thirteen years later.

O. T. SCHULTZ.

COLPOSCOPIC DETECTION OF CRIMINAL ABORTION. HANS HINSELMANN, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **16:14**, 1930.

Colposcopic examinations are urged for all cases in which criminal abortion is suspected, since definite or characteristic changes in the cervix uteri, such as instrumental injuries, scar, etc., may be found during life. This fact is well illustrated by two cases.

E. L. MILOSLAVICH.

DEATH BY BURNING. L. WACHHOLZ, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **16:18**, 1930.

This is a medicolegal analysis of accidental, suicidal and homicidal deaths by burning. Suicide by burning seems to be more frequent than generally is assumed. Fourteen cases of suicidal burning are reported, twelve involving women, and two, men. Four of the women were insane; the other eight, among them two prostitutes, committed suicide by burning after passionate quarrels with lover or husband. The two men, sufferers from alcoholism, committed the act while intoxicated. In instances of suicide, the body is found, as a rule, in a prone position, as the person tries to protect his face from the flames. Three cases of murder by burning are presented in an interesting manner and the circumstances analyzed.

E. L. MILOSLAVICH.

GLIOMA AND TRAUMA. OTTO BECKMANN, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **16:26**, 1930.

To establish a direct relation between tumor of the brain and injury, one must carefully consider the following important criteria: 1. The injury to the skull must affect the brain or the meninges. 2. Symptoms of the injury must be evident during life and proved at autopsy. 3. A certain interval of time should elapse between the trauma and the occurrence of the tumor. 4. The tumor should be found at the site of the injury or in the direction of the coup-contrecoup action. 5. The character of the growth should be determined microscopically. Five cases are presented, and the literature on this subject is discussed.

E. L. MILOSLAVICH.

---

### Technical

DIFFERENTIAL WHITE COUNT IN INFANCY. CARL H. SMITH, *Am. J. Dis. Child.* **40:505**, 1930.

The differential blood count of thirty-seven normal and sick infants was studied from a supravital preparation and from fixed smears, and the observations were correlated. In forty-three of forty-eight comparative smears, the percentage of polymorphonuclear leukocytes was higher, and that of lymphocytes was lower in the living preparation than in the fixed film. The average of twenty-four counts from the group of normal infants showed the percentage of polymorphonuclear neutrophils to be 8.6 per cent higher in the supravital than in the fixed coverslip smear and almost 12 per cent higher than in the slide. The lymphocytes, on the other hand, ran 14 per cent and 11 per cent higher in the fixed smear of the slide and coverslip, respectively, than the corresponding cells of the supravital preparation. The principal reasons for this discrepancy are the unequal distribution of the cells and, especially, the failure to identify and include all fragmented polymorphonuclear leukocytes in the differential count of the fixed smear. With the supravital technic, the spread of cells is more even, trauma is reduced, and both motile and dying cells may be more readily identified. The lymphocyte has always been regarded as the predominant cell in the blood of the infant. This

observation has heretofore been based on differential counts employing the fixed smear with some modification of the Romanowski strain. While counts made from the supravital film confirm the preponderance of lymphocytes over polymorphonuclear leukocytes, it is often by no means as marked as indicated in the fixed smear. The differential count from the fixed smear may unduly exaggerate the lymphocytic percentage and convey an erroneous impression of a blood dyscrasia. In pyogenic infections, especially when associated with a leukocytosis, the differential count from the fixed smears gives at times a much lower polymorphonuclear and a higher lymphocyte percentage than expected. That this discrepancy is often due to an increased fragility of the polymorphonuclear leukocytes is evident from comparative supravital studies. In a routine differential count from the fixed smear, particularly when it is employed as an index of the patient's resistance, the extent of damage to the white cell encountered on the slide should be noted. If fragmented cells have been included in determining the individual cell percentage, mention of this fact should also be made.

AUTHOR'S SUMMARY.

THE COSTA REACTION. HENRY S. PENN, *Am. Rev. Tuberc.* **21**:684, 1930.

The Costa reaction is essentially a nonspecific reaction. Three minims of 5 per cent sodium citrate are mixed with 1.5 cc. of 2 per cent solution of procaine. To this are added 3 minims of the patient's blood. This is either centrifugated or allowed to settle for twenty-four hours. Then 1 minim of concentrated formaldehyde solution is added, and the results recorded according to the degree of cloudiness and the time required for its appearance. A heavy flocculation appearing in from one-half to one minute is rated +++++. The absence of, or only faint, cloudiness after eight minutes is said to be negative. As the result of the examination of 130 cases, the Costa reaction is considered a valuable aid in determining activity in tuberculosis, but cannot be used to determine the degree of activity.

H. J. CORPER.

RED BLOOD CELL SIZE IN ANEMIA. WILLIAM P. MURPHY and GREENE FITZHUGH, *Arch. Int. Med.* **46**:440, 1930.

The determination of the volume of the individual cells as suggested by Haden and as herein recorded is a more simple means of determining the average size of cells than is the measurement of their mean diameter. Determinations of the volume of the individual cells are helpful in differentiating pernicious anemia from other anemias in most instances in which difficulty in diagnosis might arise, the outstanding exception being in the rare condition of so-called aleukemic leukemia. During and shortly following acute loss of blood, there is an increase in the average volume of the individual cells, whereas in anemia resulting from chronic loss of blood, it is generally low. Figures presented suggest that with the adequate administration of liver, the red blood cells of patients with pernicious anemia return to normal volume. A figure for the volume of individual cells greater than normal should indicate inadequate treatment. Not only is the method for determining the volume of the individual cells a simple one to use, but the information so obtained is also as reliable as is that obtained by measurement of the mean diameter of the red blood cells by the method used.

AUTHORS' SUMMARY.

STAINING NERVE FIBERS IN MOUNTED SECTIONS WITH ALCOHOLIC SILVER NITRATE SOLUTION. H. A. DAVENPORT, *Arch. Neurol. & Psychiat.* **24**:690, 1936.

Davenport describes his new method of staining celloidin or paraffin sections with silver. The former are mounted on slides with albumin fixative and plunged immediately into a 2 per cent solution of celloidin. When the edges of the original celloidin soften, the slide is removed, drained quickly, inverted and tilted back and forth, and laid face up until the coating sets. Before the drying of

the surface begins, the specimen is put into a solution of 80 per cent alcohol. After a few minutes, it is ready for the silver bath—a solution of 10 per cent silver nitrate in 85 per cent ethyl alcohol slightly acidified with nitric acid (from 5 to 7 drops of a 7 per cent concentrated aqueous solution of nitric acid to 50 cc. of the silver solution). The sections remain in the latter approximately one hour or longer until a light brown tint appears in the tissue. After removal from the silver bath, the section is rinsed quickly in strong alcohol (from 95 per cent to absolute) and reduced in an alcoholic solution of a mixture of formaldehyde and pyrogallol; the intensity of reduction is judged by the intensity of the brown color. Then the sections are passed through two or three changes of 95 per cent alcohol, absolute alcohol, xylene and Canada balsam (from 2 to 3 minutes each).

The mounted paraffin sections are treated in the same manner, but first they should be passed through xylene, absolute alcohol and alcohol-ether.

With the method outlined, Davenport demonstrated nerves and end-plates in the voluntary muscles of the cat and the nerves in the spinal cord of man and dog; however, the fibrils and synoptic end-loops could not always be demonstrated, while the finest fibers of the gray substance could not be demonstrated at all.

G. B. HASSIN.

THE TAKATA-ARA COLLOIDAL TEST WITH SPINAL FLUID. LOUIS J. KARNOSH and HAROLD N. KING, Arch. Neurol. & Psychiat. **24**:743, 1930.

The Takata-Ara's method—1 cc. of spinal fluid plus 1 drop of 10 per cent solution of sodium carbonate solution, plus 0.3 cc. of equal parts of a 0.5 per cent solution of corrosive sublimate and 0.02 per cent fuchsin solution—causes no changes in the color of a normal spinal fluid, the mixture remains clear and violet. In cases of tabes and dementia paralytica, it becomes cloudy and a precipitate forms. In meningitis the fluid becomes red.

In testing this method Karnosh and King compared the results they obtained with the colloidal reaction of the gum mastic. The cerebrospinal fluids tested were taken from patients with dementia paralytica, senile dementia, arteriosclerotic brain disease, alcoholic psychoses, manic depressive insanities, schizophrenia and various other psychoses and organic brain diseases. Altogether 180 cases were studied. The conclusions are that the test is not specific; it has no advantages over similar tests such as Weichbrodt's; it is positive in 82 per cent of the cases of so-called metasyphilis, and it is frequently positive in cases of arteriosclerosis, trauma or tumors of the brain.

G. B. HASSIN.

THE USE OF ACID FUCHSIN IN RUSSELL'S TRIPLE SUGAR MEDIUM. G. D. CUMMINGS, J. Infect. Dis. **47**:359, 1930.

The preparation of Andrade indicator as outlined in the literature is unnecessary, since undecolorized acid fuchsin may be used with equal success. Andrade indicator as generally prepared contains enough normal sodium hydroxide to decolorize the acid fuchsin present and to have a decided effect on the  $pH$  of the medium to which it is added. A 1 or 2 per cent concentration of aqueous acid fuchsin used in 1 per cent amounts in the Russell medium gives clearcut and correct reactions with the following five organisms when incubated for twenty-four hours at 37 C.: *Eberthus typhosus* Rawlings, *Salmonella paratyphosus* A, *Salmonella paratyphosus* B, *Eberthella dysenteriae* Shiga, and *Escherichia coli-communior*. The finished medium has sufficient pink color to indicate the production of alkali. Undecolorized acid fuchsin is recommended for use in the Russell medium, because of its chemical stability, ease of preparation, ability to give clearcut reactions and lack of inhibitory effect. The use of undecolorized acid fuchsin for the preparation of Andrade indicator would eliminate the variety of methods now to be found in the literature.

AUTHOR'S SUMMARY.

STAIN FOR RICKETTSIA BODIES. M. RUIZ CASTANEDA, J. Infect. Dis. **47**:416, 1930.

A buffer formaldehyde solution is prepared as follows: *A*. 23.86 Gm. of sodium phosphate is dissolved in 1 liter of distilled water. *B*. 11.34 Gm. of monopotassium phosphate is dissolved in 1 liter of distilled water. Thirty-eight parts of *A* and 12 parts of *B* are mixed and filtered through a Berkefeld candle; 0.2 per cent of formaldehyde is added as a preservative. The buffer solution should have a  $p_H$  of 7.6. The stain is made as follows: 20 cc. of buffer solution; 1 cc. of formaldehyde; 3 drops of Löffler's methylene blue (methylthionine chloride, U. S. P.) or 10 drops of 1 per cent methylene blue. Stain with this mixture for two or three minutes. After washing the slide with running water for thirty seconds, the counterstaining is done with aqueous safrain for one or two seconds.

EDNA DELVES.

THE STAINING OF CALCIUM. G. R. CAMERON, J. Path. & Bact. **33**:929, 1930.

Silver nitrate is not a test for calcium or phosphate; the black reaction is given by a variety of solid deposits of which the anion is more important than the metal. Alizarin is a nearly specific stain for calcium. It reacts readily in vitro and in vivo with recently deposited calcium phosphate or carbonate, normal or pathologic, but often fails to stain older deposits. This limits its practical utility. Hematoxylin does not stain calcium salts, although it often identifies areas in which changes favorable to the deposition of calcium salts are taking place. The reaction obtained in these areas depends partly on the presence of iron and mostly on a peculiar ground substance which is normally present in bone and cartilage and which also appears at the site of pathologic calcification and, mordanted with aluminium or chromium, stains deeply with hematoxylin.

AUTHOR'S SUMMARY.

ASCHHEIM-ZONDEK TEST. G. ADDESSI, Clin. obstet. **32**:449, 1930.

From the application of the Aschheim-Zondek test to forty-eight pregnant women, in various months of gestation, forty-seven positive results and one negative result were obtained. Of eight women with extra-uterine pregnancies, six gave a positive reaction and two a negative reaction. In sixteen puerperal women it was demonstrated that the hormone of the anterior lobe of the hypophysis is eliminated with relative rapidity, for after the sixth day following the birth the reaction was always negative. In twenty-four women of various ages with various gynecologic disorders, healthy men of various ages and others employed as controls, the result of the test was always negative. The importance and the utility of the test are emphasized, especially in those cases of initial pregnancy in which the clinical examination oftentimes does not furnish sure results.

A NEW METHOD FOR THE EXAMINATION OF THE SMOOTH MUSCULATURE OF THE LUNG. A. LUISADA, Beitr. z. Klin. d. Tuberk. **73**:657, 1930.

A method is presented by which the contractions of the smooth musculature in the lung can be recorded by a method similar to that used in making an electrocardiogram. Electrograms were recorded of animals under normal condition, after the resection of the vagus nerve, after stimulation of the vagus and sympathetic nerves and under the influence of various drugs that act on the neuro-vegetative system. During the anaphylactic shock, the contraction of the smooth musculature is constantly increased, and a lack of correlation exists between the smooth and striped respiratory musculature. The method was elaborated in such a way that human electrobronchograms could be recorded. One electrode is applied to the trachea and another to a small bronchus.

MAX PINNER.

PREVENTION OF THE FORMATION OF MOLDS IN KAISERLING II SOLUTION. A. GAÁL, *Centralbl. f. allg. Path. u. path. Anat.* **49**:97, 1930.

The addition of 1.5 cc. of liquid carbolic acid to each liter of Kaiserling II solution prevented the formation of molds for at least three years. There was no alteration of color in the specimens.

GEORGE RUKSTINAT.

A METHOD FOR THE SAMPLING OF ALVEOLAR AIR IN MAN. M. E. MARSHAK, *Ztschr. f. d. ges. exper. Med.* **72**:32, 1930.

A method is described by which samples of alveolar air may be collected over mercury. Samples collected by this method apparently contain a higher percentage of carbon dioxide than alveolar air collected over acidulated water.

PEARL ZEEK.

## Society Transactions

### NEW YORK PATHOLOGICAL SOCIETY

*Regular Meeting, Nov. 19, 1930*

LEILA CHARLTON KNOX, *President, in the Chair*

#### HEMORRHAGE INTO THE PERICARDIUM FOLLOWING RUPTURE OF A CORONARY ARTERY. CHARLES T. OLCOTT.

A specimen of a heart was presented in which there had been a rupture of the circumflex branch of the left coronary artery with resulting hematopericardium. There was no aneurysm. The patient was a man, aged 60, who had previously been healthy. The symptoms suggested angina pectoris. There was an interval of fifteen hours between the first symptoms and death.

In a fairly complete review of the literature, only thirty other cases were found in which the lesion was clearly due to coronary rupture, and in which the surrounding myocardium was normal. Sixteen cases were unassociated with aneurysm, while in fifteen aneurysm was found. The etiology seems to have been atheromatous in fourteen cases (ten without aneurysm); due to infectious embolism in five cases (four with aneurysm), and due to syphilis in two cases, both with aneurysm. Nineteen cases occurred in males, and eleven in females. The average age of the patients with atheromatous conditions was 65 years, of those with infectious embolism, 19.2, and of those with syphilis, 46. Rupture occurred in the left artery eleven times, in the right artery eight times and in both arteries three times.

This article will be published in full in *The New England Medical and Surgical Journal*.

#### DISCUSSION

HELEN S. PITTMAN (by invitation): We performed an autopsy on a Greek woman somewhat over 60, who came to St. Luke's Hospital about 6 a. m. and died before reaching the ward. She spoke very little English, as did the people who were with her, so that the history is incomplete. She had awakened at 1 o'clock that morning with severe pain in the upper part of the abdomen, with some radiation to both arms. She was examined while in a moribund condition, and died almost immediately. Autopsy was performed about three or four hours after death, and the pericardium was found distended with blood and fresh clots. There were three lacerations in the epicardium on the posterior surface of the tip of the left ventricle, and there was a diffusion of blood in the subepicardial tissue. When the left ventricle was cut open, it was seen that there was a fresh hemorrhagic infarct in the tip of the left ventricle, and the probe passed through the epicardium came out on the surface. There was extensive arteriosclerosis with calcification. The base of the mitral ring measured about 4 mm. across and was solidly calcified. Both coronary arteries were calcified throughout, and up to the present time no rupture of the vessel has been found. The heart is now being hardened for section.

CLARENCE DE LA CHAPELLE: I have seen three cases of ruptured coronary artery; two were from the service of the chief medical examiner, Charles Norris, and were from patients of unknown age. The age of one patient was guessed to be 55. He had syphilitic aortitis and an aneurysm of the left coronary artery near its origin, which had perforated through the wall of the left auricle. A man, whose age was guessed to be 60, had a rupture of the left circumflex branch about the

midportion; his arteries were markedly sclerotic. In both of these cases a history was not obtainable. The third case was a hospital case; a Negro, aged about 21, entered the hospital with signs of cerebral hemorrhage. At postmortem examination we found the cerebral hemorrhage, but we also found a ruptured descending branch of the left coronary artery. Marked hypoplasia of the aorta and other signs of status lymphaticus were present. These are the only three cases I have seen at Bellevue Hospital.

GENERALIZED AMYLOIDOSIS: REPORT OF A CASE. DUNCAN McCUAIG (by invitation).

The presenter described a case of advanced generalized amyloidosis discovered at autopsy in a woman, aged 64, from whose history as well as postmortem examination none of the usually ascribed, associated, chronic, cachectic states was discovered. Polycythemia was present. In a review of the literature, McCuaig discovered only one similar case. He attributed the polycythemia to stasis of the blood resulting from an extreme degree of amyloid deposition in the organs. The earlier and the more recent experimental work on the artificial production of amyloidosis in animals was described.

DISCUSSION

MENDEL JACOBI: Some of the work of Jaffe in Chicago with the use of cholesterol and other lipoids in preventing the formation of amyloid was mentioned. In this connection I should like to call attention to the marked differences between Jaffe's results and those of Smetana and Kuczynski in obtaining amyloid in nonprotected animals; the latter regularly obtained amyloid after from seventeen to thirty injections of nutrose (sodium caseinate), whereas the former required from forty to sixty injections and delayed its formation only up to seventy injections.

I should also like to call attention to a paper presented at the Academy before the Society for Experimental Biology and Medicine by Dr. Grayzell and myself dealing with this problem. We produced amyloidosis in white mice kept on an ordinary laboratory diet, or one to which meat had been added, after from seventeen to twenty-six injections of nutrose, whereas only a few changes dimly suggestive of amyloid were produced after fifty-five injections into mice kept on a diet to which liver extract had been added, and definite changes were not apparent until the sixty-eighth injection. Even in these animals the amyloid was present in far lesser quantities and in more fragmentary arrangement. With Smetana, we found the earliest amyloid in the cells of the reticulo-endothelial system, rather than as an extracellular deposition.

PATHOGENESIS OF HYPERNEPHROMA. DAVID PERLA and J. GOTTESMAN.

An analysis of forty-four instances of hypernephroma from a clinical and pathologic point of view was made. Of these, sixteen instances were accidental observations seen at autopsy.

All gradations from benign structures to malignant hypernephroma were found in the same tumor.

All types of histologic variations may occur in the same tumor, such as cortical adenoma, typical hypernephroma, papillary and adenomatous forms and highly malignant carcinomatous and sarcoma-like infiltrations.

Comparative studies emphasize the histogenetic development of hypernephroma from cortical aberrant tissue. Cortical suprarenal rests in the kidney may grow into benign adenomas. At any period during the life of the individual such benign structures may become malignant. This development and subsequent metastatic dissemination proceed at a variable rate.

The neoplasm may exist for many years prior to the onset of symptoms.

There is extreme variation in the interval between the onset of symptoms and the death of the patient from the neoplasm.

In about half the cases the primary symptoms of neoplasm were referable to metastatic lesions, such as the pelvis, skull, long bones, vagina and lungs.

Primary malignant neoplasm of the kidney with metastatic foci may exist for some time prior to the development of any symptoms.

## DISCUSSION

M. A. GOLDZIEHER: This presentation of the subject has drawn attention to the appearance of pleomorphic tumor cells in the Grawitz tumors, as well as in the suprarenal cortical tumors. Nevertheless, the arguments and the pictures presented, beautiful as they are, do not convince me that the morphologic evidence presented by Stoerk and some of his followers may be disregarded. It would take too much time to go into the morphologic discrepancies between the opinion of Stoerk and that which we have heard. I want to draw attention to some of the biologic aspects of the question, which to my mind have at least as much weight as the morphologic considerations. One of these is a point that Lubarsch himself has raised, when he admitted that it was peculiar that the Grawitz tumors are rich in glycogen, whereas the cortical suprarenal tumors do not contain glycogen. Furthermore, I have seen cases of renal lipoidosis, particularly in infants suffering from some nutritional disturbance, in which the cells of the kidneys were so engorged with fat that they resembled most closely the cells presented, as typical suprarenal cortical cells. Finally, and this is the most important point, in all the cases of suprarenal cortical tumors that I have seen, and that is quite a number, and in all the cases reported in the literature, with few exceptions, there is evidence of transformation of the sex character of that person, particularly if it is a woman. This action of the suprarenal cortical tumors is not present in Grawitz' tumors of the kidneys. In none of them did I ever see any transformation of sex character, and to my knowledge there is no such observation recorded in the literature. However, tumors of the suprarenal cortex, both benign and malignant, are capable of transforming the sex character of the female in almost every case. Even the small adenomas frequently found in the cortex of old women are most probably responsible for the so-called old woman's beard, as I never fail to find them whenever I do an autopsy on an elderly woman with a hairy face. Yet tremendous tumors occurring in the kidney with or without metastases never produce such changes. I think that we are too much impressed by the morphologic similarity of the typical Grawitz tumor cells to suprarenal cortical cells, particularly in view of the fact that this similarity is restricted to the large foamy cells and does not hold as to the other cells of the small dense type, which are never absent in suprarenal cortical adenomas. Moreover, the polymorphism of the suprarenal cortical cells that has been emphasized here, and which I certainly admit, does not go so far as to produce real lumina with papillae. I also failed to see, in the demonstration here at least, what we would all admit to be papillary structures; therefore, I remain unconvinced of the suprarenal cortical origin of Grawitz' tumors, nor do I believe that they originate from suprarenal cortical cells, but rather from the renal epithelium. Finally, I want to mention that I have seen a few cases of renal cortical adenomas, in which I could follow a series of changes from the unquestionably renal adenoma type to a type somewhat similar to the so-called hypernephroma.

PAUL KLEMPERER: I think that it is hardly necessary for me to add to what Dr. Goldzieher said, but I should like to make my standpoint clear. I agree with Dr. Perla and Dr. Goldzieher that it is extremely difficult to settle the question as to the origin of the Grawitz tumor from the mere histologic evidence. I should like only to ask the question, On whom should actually fall the burden of proof that the Grawitz tumor originates from one of the tissues concerned? I do not think that it is correct to ask only the men who do not believe that the Grawitz tumor of the kidney originates exclusively from aberrant suprarenal tissue to prove that it originates from renal tissue. Actually, the proof should be shown by the men who believe that the Grawitz tumor originates from misplaced supra-

renal tissue. Is it not a rather peculiar fact that the overwhelming number of benign and malignant renal tumors should always originate from an aberrant tissue, and not from the homeotypical tissue? I think that this argument alone speaks in favor of the men who believe that the Grawitz tumor originates not from aberrant suprarenal tissue alone, but at times from the renal parenchyma.

From my studies of tumors of this type I have come to a conclusion opposite to that of Dr. Perla and Dr. Gottesman. They reached the conclusion that a tumor is of suprarenal origin in spite of the presence of glandular structures, for they have found areas in which the tumor apparently takes the structure of the fascicular zone of the suprarenal. I think just the opposite. In examining these tumors, whenever I find an area in the section that apparently simulates suprarenal tissue, I look further. I am not satisfied to make the diagnosis of hypernephroma in a case in which I find evidence of glandular structures. I have never seen a benign or a malignant tumor of the suprarenal that had glandular structures, and I was not convinced from the pictures presented that the one tumor of the suprarenal presented showed actual glandular formation. One point that is always brought up in favor of the possibility that suprarenal tissue might become incorporated in the renal anlage is the close vicinity of both structures during embryonal life. I do not think that this is proof, or that there is any definite conclusion one might draw from this embryologic fact. Why do we not find just as frequently the same type of tumors in the testis or in the ovary, which after all in embryonal life are in close vicinity to the structure that later becomes the suprarenal gland? From the mere fact of the presence of large, clear cells, I do not think that one can make the diagnosis of hypernephroma, because they will be found in all possible locations. One tumor that was described years ago as a hypernephroma of the thyroid was most probably a parathyroid tumor. I have seen carcinomas of the breast which showed similar cells. It is well known that metastases often show structures very different from those of the primary tumor, and I think that we can often identify the true structure of the primary tumor from the metastases. To my mind, this experience explains the fact that Dr. Perla and Dr. Gottesman encountered tumors which in their primary location in the kidneys simulated suprarenal cortex, whereas the metastases exhibited glandular structures. I would not say that I consider it impossible to have a Grawitz tumor of suprarenal origin, but I doubt that it is frequently so.

ALFRED PLAUT: I agree with the statements of Dr. Goldzieher, and as Dr. Klemperer just said, it is dangerous to make a definite diagnosis of a tumor because the tumor is mainly composed of large, clear cells. One of the arguments in favor of the hypernephric origin of Grawitz' tumors has been seen in the frequent location of Grawitz' tumors in the same regions in which aberrant suprarenal tissue is found. The ovary and the broad ligament belong to these regions; however, while aberrant suprarenal tissue is much more frequent in the ligament, the tumors in question occur much more frequently in the ovary. I had the opportunity of examining a large, solid, yellow, ovarian tumor that had been diagnosed by several physicians as a hypernephroma of the ovary. Examination of many blocks, however, finally led to a small part of the tumor which was a distinct fibro-epithelioma with small, narrow cells containing dark, small nuclei. While it is easy to understand how such small cells may become large, clear cells such as are found in the Grawitz tumor, by storing any soluble substances in the cytoplasm, I feel unable to see how such large, clear cells may be transformed into small ones. I may be permitted to take exception to the often repeated statement of the transformation of these large, clear cells into other epithelial cells with more compact cytoplasm. Thus, we cannot assume that the multiform picture of the tumors in question can be explained by secondary changes in cells that originally were large, clear cells. They probably came from cells that originally had quite a different aspect.

DAVID PERLA: In reply to Dr. Goldzieher, I do not want to go into this study in a controversial way; it is endless, and we could argue both ways just as readily.

One can see certain structures, and from them make certain deductions. I do not believe in laying too much stress on pure morphology. The two patients with tumors in the suprarenal glands showed no changes in the sex characters. There were no accompanying symptoms of virilism. Tumors in the suprarenal gland are frequently associated with virilism, but to say that a tumor arising in a cortical rest is not a hypernephroma because it was not accompanied by physiologic changes carries no weight. We know that malignant tumors of the thyroid gland are not necessarily associated with hyperthyroidism. There can be extensive malignant tumors of the thyroid with widespread metastases and certainly no manifestations of functional change can be seen. As to aberrant tissue being found in other areas without tumors corresponding to hypernephroma, I can say only that if one denies that there is such a thing as hypernephroma, it is useless to argue about it. The three discussers have given me the impression that they believe that there is no such thing as a hypernephroma, but when we find tumors with large, foamy cells resembling aberrant cortical tissue, it is not without reason to assume that they might arise from such an aberrant tissue. Hypernephroma of the testis has been reported, and we know that the testis is the site of the aberrant tissue. It has been reported in the liver, where aberrant tissue has occasionally been found.

As to the variations in structure, I did not mean to imply that actually a large, foamy cell transformed itself into a small hyperchromatic cell, but that if you see a number of cells with all gradations of the quantity of lipid material in the cell and all gradations of the quantity of fluid in the cell, some being extremely hydropic, others having the characteristic fatty appearance with a kind of network, others showing less lipid and still others showing no lipid, staining homogeneously and definitely showing less cytoplasm, it is conceivable that all have had a common origin. The variation of the fluid in the cell, the variation of lipid and even the quantity of glycogen in a cell do not detract from the original source of that cell. I think that the presence of lipid and fluid in a cell depends on accidental physico-chemical conditions.

THE PATHOLOGIC AND PHYSIOLOGIC ASPECTS OF SIMPLE GOITER AS PRODUCED  
EXPERIMENTALLY IN RABBITS. BRUCE WEBSTER (by invitation).

For the past fifty years various attempts have been made to produce simple goiter experimentally with a view to discovering its etiologic factor. A few of these attempts have been partly successful. Notable among these are the goiters produced by Wegelin with cracker crumbs, by McCarrison with bacterial toxins and by Marine with liver and fats. In each of the foregoing instances, the amount of hyperplasia was not great, and the time required was long.

In the winter of 1927 thyroid enlargement was noticed among the rabbits that were being used for experimental syphilis at the Johns Hopkins Hospital, Baltimore. It soon became apparent that all animals maintained in the laboratory for more than four weeks showed an increase in the weight of the thyroid gland. This increase continued in direct proportion to the length of time that they were kept in the laboratory. These animals were being maintained under a standard laboratory regimen similar to that used in many other institutions. The diet consisted of 250 Gm. of cabbage daily, and 50 Gm. of oats and 20 Gm. of hay once a week. All the animals were free from goiter on admission to the laboratory. Their nutrition was well maintained, the body fat being abundant. Except for an increase in the size of the thyroid gland, the animals were essentially normal at autopsy. There was a slight tendency toward an increase in the average heart: body-weight ratio.

Controlled experiments were carried out which established the fact that the cabbage in the diet was the causative factor in the production of goiter. Marine and his associates confirmed this observation and further demonstrated that all members of the *Brassica* group of vegetables were goitrogenous, while other closely related groups were relatively nongoitrogenous.

During the course of this work it became apparent that during the winter months (from October to March) goiter was more easily produced than during the

summer months. A reanalysis of the data showed that this had been the case since the work was begun at Baltimore in 1927. By a series of elimination experiments, it was possible to show that this seasonal variation is due to a seasonal change in the cabbage itself and not in environmental factors affecting the animal. Further, it was demonstrated that this seasonal variation occurs irrespective of any seasonal variation in the iodine content of the cabbage. The loose, rapidly maturing summer cabbage was found to be nongoitrogenous, irrespective of iodine content or source. The mature, slowly growing, so-called winter varieties manifest varying degrees of goiter-producing power. For the past two years, some change has occurred in late autumn which causes an abrupt increase in the goitrogenous power of cabbage grown under standard conditions. Attempts to correlate this with meteorologic changes so far have been unsuccessful. Cabbage of the slowly maturing variety imported from Holland has been found to be extremely goitrogenous. There was some evidence that there was a yearly as well as a seasonal variation in the goiter-producing power of cabbage.

In association with Dr. Marine, experiments were carried out to determine the nature of the substance in cabbage which produces goiter. The first question that arose was: Is the goitrogenous factor a positive one or a deficiency phenomenon? Repeated experiments showed that when an active goitrogenous cabbage was dried, either in air or in vacuo, it lost completely its goiter-producing power. Certain extractives had the same effect. These observations tend to suggest that a positive and not a deficiency factor is present.

Little has been found concerning the nature of this substance. Steaming the cabbage for thirty minutes tends to increase its goiter-producing power. If the steamed cabbage is pressed, the residue or cake contains all the goiter-producing material, while the juice contains none. The substance is not readily soluble in water, either at room temperature or at 100 C. Mild acid hydrolysis does not destroy this substance. Alkaline hydrolysis may destroy it to a slight extent.

Marine has expressed the idea that whatever the nature of this substance may be, it acts through the oxidation-reduction systems of the body, creating an increased demand for thyroxin and thus bringing about thyroid hyperplasia in an effort to meet this demand.

Pathologically, the goiter produced by cabbage is a simple hyperplasia of the thyroid gland, similar in type to all other simple goiters in man and animals. Glands weighing as much as 40 Gm. (approximately 400 times the normal size) have been encountered in rabbits. The vascularity of these glands was great. The enlargement was always diffuse. Gross nodules were not encountered.

Microscopically, the typical picture was that of struma diffusa parenchymatosa. Because of the small size of the follicle of a rabbit's thyroid gland, infoldings were rarely observed. The acinar epithelium was increased in height and the cells were predominantly of the chief type. The nuclei were large and vesicular. There was almost complete absence of colloid in all goiters of any appreciable size.

In rabbit goiters of less than a year's duration, adenomas were not observed. Marine expressed the opinion that adenomas rarely occur spontaneously in animals. The idea suggested itself, however, that it might be possible to produce so-called "involutionary adenomas" in rabbits by repeatedly causing the thyroid gland to become alternately hyperplastic and then involuted. Accordingly, three years ago, a number of young rabbits with large goiters were set aside for this purpose. Since that time they have alternated between periods of a cabbage diet and periods of iodization. In this way the attempt was made to reproduce the cycle of alternate hyperplasia and involution which takes place in an area of endemic goiter. These animals began to die of senility and the thyroid glands showed typical so-called "involutionary adenomas." The circulation was greatly distorted by areas of persistent hyperplasia and colloid cysts. There was an increase in stroma. In short, the condition resembled the early stages of a struma nodosa, such as occurs in particular areas.

Goiters produced experimentally in this way were used as a source of material for various studies of simple goiter. The metabolism was studied in a series of

animals. It was found that those with large goiters had a metabolism approximately 16.6 per cent lower than that of normal animals of the same age. Later the development of goiter was observed in a group of animals; their metabolism fell from normal to a point almost at the level produced by total thyroidectomy. The animals showed changes in the skin and hair typical of mild myxedema. Once this low level of metabolism was reached, it remained constant for as long as a year, provided the patient was not treated for goiter.

The effect of the administration of iodine to these animals was then studied. Rabbits with large goiters were given intraperitoneal injections of 25 mg. of potassium iodide daily. They lost weight rapidly, the thyroid glands decreased appreciably in size and the animals died in from two to seven days. Before death, their metabolism rose markedly, often to two or three times the normal level. At autopsy, the thyroid glands were in various stages of involution, depending on the period that had elapsed between the administration of iodine and death. By reducing the quantity of iodine administered, it was possible to cause an increase of metabolism which gradually subsided to a normal level. The administration of iodine to normal rabbits causes little or no change in the production of heat.

This increase of metabolism was regarded as a possible means of obtaining information about the quantitative relationship between available inorganic iodine and the hormone into which it is elaborated. On the basis of Marine's observation that 1 Gm. of hyperplastic thyroid gland is capable of absorbing 1 mg. of iodine, the metabolic changes produced by single minute quantities of iodine were studied. Briefly, these experiments suggested that in hyperplastic glands the quantity of thyroid hormone elaborated (as indicated by the changes in heat production) appeared to vary directly, within certain limits, with the amount of the available inorganic iodine.

By the injection of varying amounts of iodine, and by frequent biopsies from the glands, it was possible to study involution under controlled conditions. The degree of involution, as would be expected, depended on the amount of available iodine, together with the time that it was allowed to act. By varying these two factors, it was possible to obtain all stages from complete hyperplasia to a colloid goiter, or complete involution, at different times in the same animal. The injection of as little as 1 mg. of potassium iodide produces striking changes in the microscopic picture of these goiters. There is a rapid transition from the chief type of acinar cell to the colloid type. This suggests that these two types of cells, described by Langendorff, are in reality two phases of activity of the same cell.

An excess of iodine (7.5 mg. per week) will completely prevent the development of goiter, irrespective of the potency of the cabbage fed.

In summary, the reactions given by this type of experimental goiter are essentially the same as those exhibited by simple goiter in man. Perhaps the only difference is the severity of the reaction observed when iodine is administered to animals with large goiters. This may be analogous to the increase in metabolism reported in various instances after the liberal use of iodine in areas of endemic goiter.

The foregoing material was presented largely as a method of producing goiter experimentally in a laboratory animal, under controlled conditions, with the hope that by means of this method some light may be thrown on the still unsettled question of the etiology of simple goiter.

#### LIPOID NEPHROSIS. PAUL KLEMPERER AND (by invitation) A. B. KANTROWITZ.

Two cases of pure lipoid nephrosis were presented. In one, that of a man, aged 48, repeated urinalyses gave negative results, during the course of anti-syphilitic treatment; a generalized edema developed suddenly. Death occurred after the onset of erysipelas at the site of drainage by Southey tubes. In the other case, that of a boy, aged 2½ years, edema developed three months prior to his admission to the hospital. Death resulted from peritonitis, pneumococcus type IV being found in the blood stream and peritoneal fluid. Examination of the kidneys by the ordinary histologic methods—hematoxylin and eosin and

sudan stain—substantiated the clinical diagnosis of lipid nephrosis. The epithelium of the convoluted tubules in both cases was swollen, containing neutral and doubly refractile fat in the basal portions of the cells, while the hyaline droplets were found in the portions nearer the lumen. The glomeruli appeared normal.

A recent paper by E. T. Bell recommending the use of special staining methods necessitated a review of both of these cases. The application of the Heidenheim azo-carmin and the Lee-Brown modification of the Mallory aniline blue-orange G stains resulted in the recognition of finer histopathologic details, mainly within the glomeruli. A moderate degree of swelling of the glomerular endothelial cytoplasm and occasionally of its basement membrane was noted, especially in the second case. The swelling was caused by fine, neutral, fat droplets, also doubly refractile fats. In no case was there cellular exudation or glomerular epithelial or endothelial nuclear numerical increase. While the importance of the endothelial swelling cannot be minimized in glomerulonephritis, it must not assume an undue position in the absence of the other criteria of inflammation.

It was agreed with Bell that his recommended staining methods result in bringing out finer histologic details; however, the presenters disagreed with his conclusion that lipid nephrosis is a mild type of glomerulonephritis with only incomplete obstruction of the glomerular capillary loops, since in both cases presented the glomerular observations did not justify a diagnosis of inflammation.

This article will be published in full in *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*.

#### DISCUSSION

IRVING GRAEF: I should like to ask Dr. Klemperer if he would carry his analogy between the storage of "fat" in the glomerular endothelium seen in his second case and the storage of "fat" seen in Niemann-Pick's disease to the point where he would postulate that such storage might lead to proliferation of the endothelial cells.

PAUL KLEMPERER: I think that regeneration following degeneration within the glomeruli, as in the tubular epithelium, may occur, but even then the proliferation will be only a reparative phenomenon.

M. A. GOLDZIEHER: The last words of Dr. Klemperer make it almost superfluous for me to say what I have in mind. I think that the whole point of Dr. Bell's criterion for the evidence of inflammation is the large number of nuclei. Whether in this case there are more nuclei than normally is a matter of opinion. I could not see more than in any ordinary glomeruli. However, it is not fair to make a judgment on the evidence of photomicrographs, however excellent they be. If we see more nuclei, it is important to distinguish what kind of nuclei they are. Dr. Bell mentioned that there were many hematogenous cells. I could not see them. The cells are either epithelial or endothelial. Let us take it for granted that in these cases of lipid nephrosis more endothelial cells are found. Any one who is familiar with the extensive deposit of lipid material in endothelial cells knows that, at a certain stage, these cells start to proliferate. After all, we know that proliferation is not the attribute of inflammatory lesions alone. Proliferation of endothelial cells is also an expression of a type of lesion of non-inflammatory origin. So in advanced lipid nephrosis there may be hyperplasia of the endothelial cells, which to my mind would be no proof of the inflammatory nature of these lesions. In order to accept a lesion as inflammatory, I think that all pathologists, perhaps with the exception of Dr. Bell, admit that there must be more than hyperplasia of the endothelial cells. There must be cells of the leukocytic type, or, at least, if there are no leukocytes, there must be lymphocytes or some other hematogenic cells customarily seen in inflammatory conditions. Finally, an inflammatory process is not complete from its morphologic aspect if we do not see cell damage, and the storage of fat is not sufficient evidence of the impairment of a cell. Without these three basic criteria, the impaired cells, the exudation and the proliferation, I should not be prepared to accept the lesion as inflammatory.

*Regular Meeting, Dec. 17, 1930*

LEILA CHARLTON KNOX, *President, in the Chair*

INJURIES OF THE PONS. B. M. VANCE.

The most common manifestation of injury to the pons is the presence of multiple small hemorrhages in its substance. In 328 cases of fracture of the skull, multiple pontile hemorrhages were demonstrated in 70, or 21.3 per cent. Similar lesions were found in 5 cases of injury of the head without fracture of the skull.

An analysis of these cases shows that the force that produced the injury was applied to the lateral portion of the head in 72 per cent, to the posterior portion in 24 per cent, to the frontal portion in 2 per cent and to the top of the head in 2 per cent. Apparently the mechanism that caused the pontile hemorrhages was not the same in every instance.

The anatomic relations of the pons to the basilar portion of the occipital bone, to the tentorium and to the other segments of the brain, suggest ways in which this portion of the brain stem can become traumatized. In many instances, violence applied to the cranium drives one of the cerebral hemispheres or the cerebellum on the pons and forces it against the basilar process. At other times, a lateral impact may cause the pons to injure itself against the sharp edge of the tentorium.

A case is shown in which the pons was practically severed by a lateral force, which drove it against the edge of the tentorium. The deceased, a white man, aged 39, was struck by an automobile; he lived six hours. The skull was not fractured. There were lacerations of the temporal lobes and the cerebellum near the tentorium, and the pons was divided except for the subarachnoid membrane and the cerebral vessels.

Among seventy-five cases of spontaneous intracranial hemorrhage, multiple pontile hemorrhages were noted as accessory in ten. Four were cases of pachymeningitis interna hemorrhagica; four were cerebral hemorrhages in the basal nuclei; one was a subarachnoid hemorrhage in the fissure of Rolando, and one was an aneurysm in the circle of Willis which had ruptured spontaneously. All these cases were associated with considerable unilateral intracranial pressure, and it is not unlikely that the tributaries of the veins of Galen which drain the pons were blocked, thus creating a condition that furthered the rupture of the blood vessels in its substance.

ALBERS-SCHOENBERG'S DISEASE. "MARBLE BONES." M. C. PEASE (by invitation), A. G. DESANTIS (by invitation), and NICHOLAS M. ALTER.

In 1904, Albers-Schoenberg reported peculiar roentgen observations of the entire bony system. In these pictures the bony structures were replaced by a homogeneous "marble" appearance, hence the name "marble bones." Subsequent reports by Sick, Lorey, Schulze, Lauterberg, Lievre, etc., emphasize the other cardinal symptoms of the disease entity. The disease can be traced back to childhood. The whole skeleton seems to be uniformly affected. After a lapse of time, the bones become fragile. These fractures of the bone may not be associated with functional disturbances of other sorts (Albers-Schoenberg, Merrill, etc.). At a more advanced stage of the disease, atrophy of the optic nerve and severe anemia occur, which may lead to a fatal outcome. As there are only two cases reported in the American literature, with no pathologic information, the present case is reported with clinical, chemical and pathologic data. The German literature contains sixteen acceptable cases with a great variety of clinical and pathologic observations.

The patient, M. P., a girl, aged 8½ months, was admitted to the New York Post-Graduate Hospital with the complaints of blindness, "rolling of eyes" (nystagmus), pallor, enlargement of the abdomen and loss of weight. At the age of 2 months, the mother took the baby to a doctor for loss of weight and

"rolling of eyes." The doctor considered the symptoms due to feeding trouble, and the baby was treated accordingly. Finally, it was noticed that the child was apparently becoming blind. The weight remained practically stationary, and the abdomen was enlarging.

Physical examination on admission to the hospital showed a frail baby girl, underweight and irritable. The head was square, the anterior fontanel four fingerbreadths in the anteroposterior directions. Examination of the fundus of the eyes showed bilateral atrophy of the optic nerves. The nose was saddle-shaped. The lower incisor teeth were erupted. There was generalized enlargement of the lymph nodes. In the distended abdomen, the liver and spleen were palpable. There had been nothing to call attention to the bones. In the hospital, the patient's weight remained practically stationary (10 pounds, 11 ounces [4.8 Kg.]). The temperature was normal, except for the last five days of life, when a terminal bronchopneumonia developed.

The conspicuous features of the laboratory examination were the anemia with leukocytosis and the calcium and phosphorus metabolic changes. There was a severe anemia of the hypochromic type, the changes of the red blood cells being as marked as in pernicious anemia. The white blood cells were considerably increased at times, and contained about 4.5 per cent myelocytes. Although the chemical examination of the blood showed nothing very striking, the amount of calcium was rather high and the phosphates rather low.

Roentgenologic examination showed fibrosclerotic thickening of all the long bones with pronounced thickening of the cortex and encroachment of the lumina of the long bones, which were of hour-glass shape. There was an old fracture near the junction of the middle and lower third of the left femur. At many places the structure of the bones was lost and had a white, "marble-like" appearance. Similar sclerosis was found at the base of the skull.

Symptoms of pulmonary involvement developed, the temperature rose, and the patient died with symptoms of bilateral bronchopneumonia.

*Abstract of Autopsy Protocol.*—The body was that of a poorly nourished female infant of 8½ months. The skin was pale. The anterior fontanel was four fingerbreadths in the sagittal direction. The costochondral junctions were swollen, resembling the rosary in rickets. The skull was sawn through with greater difficulty than in an adult on account of the extraordinary increase of resistance. The bones of the skull showed marked thickening and obliteration of the diploe. The bones of the base of the skull were also much thickened with narrowing of the foramina. The optic canal was markedly narrowed, compressing the optic nerve. The thymus, pituitary and thyroid glands were small. All the bones of the skeletal system showed marked changes. The cortex of all the long bones was markedly thickened; the outer periosteal surface was uneven, and inwardly there was transition to less dense compact bone that was replacing the bone marrow cavity. The line of ossification was irregular. In size, the epiphysis was in proportion to the enlarged end of the diaphysis. On cross-section of the epiphysis, irregular gray calcified areas were seen scattered in the blue cartilage. Subperiosteal hemorrhages were found practically over all the bones. Histologic changes were striking, as there was no resemblance to the normal bony structure. There was no definite canal system found with the characteristic concentric lamination, but an osteoid matrix that formed irregular trabeculae surrounding small cavities that were partly filled by fibrous stroma with some fibroblasts. These, however, did not form a coherent surface layer of osteoblasts. There were numerous giant cells that were not unlike osteoclasts. Cellular infiltration was present, most of the cells being of the lymphocytic type with a small dark nucleus and practically no cytoplasm. There were no granular cells.

Familial character is suggested by the cases of Lorey, Reye and Sick. The majority of the cases have been found in the earliest childhood, from a few days after birth to 5 years. In the rest of the cases an early onset of the disease is suggested with a more benign prolonged course.

The changes of the bone of the entire skeleton, although they may be of different stages, are typical, and do not suggest relationship to other diseases of the

bone. The lack of structure in x-ray pictures with the increased deposits of calcium is characteristic, and probably is the cause of the lack of elasticity and thus of the fragility of the bones. The fractures may be quite frequent and heal apparently rapidly with exuberant callus. This is also evidence of increased calcium content of the blood. Histologically, the most conspicuous features are the lack of osteoblasts, the imperfect osteogenesis with lack of lamellation and excessive calcification of osteoid tissue. There is a lack of bone marrow cavity and bone marrow formation. Many of the clinical symptoms are easily understood from these pathologic changes. The progressive anemia may lead to a fatal outcome without intervening infections. This anemia is obviously due to the lack of activity of the bone marrow, that leads to extramedullary hematopoiesis. It has even been suggested (Laurell-Wallgren, Lorey, etc.) that the enlargement of the liver, spleen and lymph nodes has the same significance as a form of compensatory hyperplasia. The increase of myelocytic cells in the blood with these organic changes resembles a leukemic condition. Such cases with generalized osteosclerosis were reported by Jaksch, Nauwerck, etc., but Jores emphasizes the difference of this type of metaplastic bone formation in the marrow from the histology of the changes of the "marble bones." The histology of these changes of the bone also excludes syphilitic and rachitic origin. In this case reported the evidence seems to be in favor of congenital abnormality of osteogenesis of the entire bone-forming system.

## DISCUSSION

M. C. PEASE, by invitation: I do not know that I can add anything to Dr. Alter's presentation, except a few more clinical details. At birth, the physician did not notice anything wrong with the baby, and at the end of three or four weeks he turned it over to one of our pediatricians as a feeding case, who cared for it for five or six months, at the end of which time it was noticed that the child was apparently blind. It was then sent into our wards. A roentgen examination was made because of the deformity of the thigh. Up to that time there was no suspicion that there was anything wrong with the bones, and the roentgen report showed this surprising condition. The roentgenogram of the skull was one of the most characteristic plates, showing remarkable thickening at the base of the skull. This child must have had a more acute case than some of those described in the literature, because the condition in the bones was not compatible with life. To be sure, she did die of bronchopneumonia, but if she had not done so, death would have occurred from inanition, and that within a few weeks.

There is another interesting thing in connection with this case. Dr. LeWald made a roentgen examination of the oldest brother of this baby for a condition supposed to be Hirschsprung's disease, but which was a dilatation of the sigmoid. In this case the bones, so far as they were included in the plates, were normal. That is interesting from the standpoint that as far as this particular case is concerned, we were not able to find any familial factor, and on further inquiry into the family history, I could find no evidence of a similar condition. At the same time, cases have been reported in which there has been unmistakable evidence of a hereditary factor.

There was little external change in the child. When I came to the autopsy room the abdomen was being sewn up. The pathologist reported that there was nothing interesting in the case, so I got the x-ray pictures, and we proceeded to do the autopsy over, and to remove some of the bones. It is not, so far as we know, a common disease. Perhaps if we watch for this condition, we may see it more frequently. It is the only case of its kind I have ever seen, but perhaps we will see it more frequently if the attention of the medical profession is called to the possibility of such a disease.

PAUL KLEMPERER: One of the main questions for me in this interesting disease is whether Albers-Schoenberg's disease should be considered as an entity, as a disease *sui generis*, or whether it should not be thought of in connection with conditions that are possibly more familiar to us, and that become more

familiar every day, since the irradiation for leukemia has become a permanent therapeutic procedure. The first cases of osteosclerosis in leukemia were reported by Askanazy a few years before Albers-Schoenberg made his first report, and he considered the osteosclerosis in his cases as a kind of natural cure for the leukemia, by which he thought that the tissues producing blood cells, instead of producing blood cells had taken up the tendency to produce fibrous tissue. Similar cases have been reported by others, and since x-rays and radium have been accepted in the treatment for leukemia, we not rarely encounter fibrosis of the bone marrow in examining the bones in chronic myeloid leukemia, which I think is related to the condition in Albers-Schoenberg's disease. Dr. Alter has emphasized that the absence of osteoblasts differentiates this condition from the osteosclerosis of leukemia. I feel, however, that it is possible that the osteoblasts are absent in a condition in which the bone formation is due to metaplasia of fibrous tissue, and in cases of leukemia treated with radiation I have seen that some of the extensive fibrous tissue, which is formed inside the bone marrow cavity and which actually more or less obliterates the bone marrow cavity, shows a tendency for deposits of calcium to become metaplastic bone. The question arises, In what way is it possible for the bone marrow to become a fibrous instead of a blood-forming tissue? I think it is not so difficult to explain if one considers the embryology of the bone marrow. In the first months, when the primitive bone marrow cavity is formed from the periosteum, blood vessels grow into the cartilage, and they are accompanied by undifferentiated mesenchymal tissue, which begins to take up blood formation, and form the early hemocytoblasts. The same tissue has the potentialities to form fibroblasts, and it depends on the stimulus which way it goes. Under roentgen treatment, apparently undifferentiated mesenchyme, which remains in the bone marrow to regenerate bone marrow during life, takes up the fibroblastic tendency and loses the hematopoietic tendency. The same occurs in these cases which have been described by Askanazy and others as osteosclerotic leukemias. In the case of Albers-Schoenberg's disease, one can only think of a congenital perversion of the undifferentiated mesenchyme, which, instead of forming blood cells from the first, forms only fibroblasts; such a congenital perversion would be one form of such an alteration of the differential potentialities of the mesenchyme, as it is expressed in the cases of leukemia under radiation treatment. It is not so surprising that the mesenchyme does not always fulfil the purpose it has under normal conditions. I remember one case of diffuse lipomatosis of the bone marrow in an adult, with severe chronic anemia. One can account for this condition in exactly the same way; the undifferentiated mesenchyme, instead of forming blood cells or fibroblasts, takes up exclusively the storage of fats, and in this way, instead of cellular bone marrow, only fat marrow is formed.

Should we not consider Albers-Schoenberg's disease a disease of the bone marrow rather than a disease of the bone? The predominance of the alteration of the blood picture in most cases possibly points in this direction. What were the changes in the spleen, the lymph nodes and the liver? Was there extensive blood formation? Was the picture one that reminded you of leukemia, or was there merely an excessive compensatory extramedullary blood formation?

NICHOLAS ALTER: I did not want to go into the explanation of what I meant by congenital absence of normal osteogenesis. I mean that there is an abnormal bone formation, and I think that is the only explanation: the perversion of the function of the bone marrow. I tried to emphasize it in the question of the histology, for I found nowhere a bony tissue of normal structure, and that feature differentiates it from the osteosclerosis, which one sees in leukemias or blood diseases of other types. There is an extensive literature on the leukemic changes of the bone in the German literature, but they all show fibrosis of the bone marrow in conjunction with the normal osteogenesis, while here the osteogenesis is entirely absent. If it were due to that explanation we ought to see cases of Albers-Schoenberg's disease more frequently. That is also one of the arguments against syphilis.

I could find no evidence in the liver and spleen of hematopoietic function. When there is a leukemic picture where the nodes are enlarged, the enlargement of the spleen and lymph node take the place of the function of the bone, but in my case it did not.

AN EVALUATION OF THE ERYTHROCYTE SEDIMENTATION REACTION AS A ROUTINE DIAGNOSTIC PROCEDURE IN THE GENERAL HOSPITAL. HELEN S. PITTMAN (by invitation).

The author gives a brief survey of the history of the sedimentation of erythrocytes. The method employed is the Westergren modification of the Fahraeus technic. The material presented includes results in 139 proved cases and 41 instances of arthritis from a series of 250 tests made on patients at St. Luke's Hospital in New York. Temperature, erythrocyte and leukocyte counts, and Wassermann reactions of the blood where available were recorded.

The series is divided into 23 controls, 41 cases of arthritis, 22 of malignant tumor, 17 of extra-abdominal infection, and 75 from patients admitted complaining of abdominal pain. The latter group included salpingitis, appendicitis, fibromyomas of the uterus, carcinoma of the stomach and pancreas, peptic ulcer and cholecystitis and cholelithiasis. The effect on the rate of intake of the food and anemia are considered. In each instance recent literature is reviewed, and table and graphs of results are shown. From this series it is felt that the following points may be made: Blood counts in cases of anemia are distorted only with a red blood cell count of less than 3,000,000. Readings below 30 mm. per hour are indicative of osteo-arthritis. Readings in excess of 40 mm. per hour point to an infectious etiology. Between 20 and 40 mm. per hour, both varieties are found. In malignant tumors the test was found to offer no diagnostic aid. The rate likewise is of no assistance in infections. In various abdominal conditions the rate is of assistance only when very much elevated above normal. Rates in excess of 80 mm. per hour have been found only with acute suppurative processes in the lower part of the abdomen or pelvis. With rates below 50 mm., all conditions in the series were represented. The test is interpreted as being of diagnostic value only in the light of other clinical and laboratory observations.

DISCUSSION

ALFRED PLAUT: The influence of anemia on the sedimentation test has been mentioned. It is astonishing to see how divergent are the opinions expressed in the literature. From my own experience I agree with Dr. Pittman's statement that only a marked anemia interferes sufficiently with the sedimentation rate so that it must be considered clinically. A slight degree of anemia has no influence. I should like to know if Dr. Pittman thinks that the rapid rate in these higher grades of anemia is due to the relative increase in the plasma protein, or perhaps to the relative increase of cholesterol, which is not infrequent in some high grade anemias. I have no personal experience concerning this, but a comparison of the chemical analysis of the blood, which may have been done for other reasons, with the results of the sedimentation test might bring out some interesting facts.

As far as the much discussed question of the differentiation between acute salpingitis and acute appendicitis is concerned, I should like to know how much time elapsed between the onset of the first symptoms and the taking of the blood. The following reason is behind this question. When a woman becomes sick with an acute pain in the lower part of the abdomen, the disease does not start at that moment. The infection has been there for some time. That means there has been sufficient time for absorption from the infectious area, which as we assume, leads to the increase in the sedimentation rate. On the other hand, when a person has pain in the right lower quadrant due to appendicitis, then we know that the infectious focus may be extremely small, and we assume that the inflammatory process is an early one, perhaps only a few hours or perhaps only one hour old. That could explain easily the fact that when one sees such a patient directly after

the onset of the abdominal pain, the sedimentation rate may be nearly normal. Therefore, in comparing the sedimentation rate in patients with appendicitis and acute salpingitis, I think one must know how much time has elapsed after the first attack of pain. I know that some people, when they see a normal sedimentation rate in spite of severe abdominal symptoms, exclude acute salpingitis, and then the remaining diagnostic points generally lead to the diagnosis of acute appendicitis. I should like to know where the surgeons of St. Luke's put the limit of operability. When everything else is normal but the sedimentation rate is high, some surgeons say "I do not operate unless it is below that point." I recall a patient who died after a seemingly safe operation, when nothing indicated any particular danger, and my opinion was asked if the sedimentation rate would have given a contraindication to operation. The chart really showed a high sedimentation rate.

As far as tumors are concerned, I wonder if one can expect a small scirrhous carcinoma to have the same effect on the sedimentation rate as, for instance, a large, ulcerating carcinoma of the intestine. I do not feel that carcinoma can be considered as an entity in its action on the sedimentation of the red blood cells.

HELEN P. PITTMAN: I am afraid I cannot tell you to what the increase in the sedimentation rate is due. I have contributed nothing to the theory of the phenomenon.

The two cases of acute appendicitis in which I found a very high rate were both in young people, one presenting symptoms for about forty hours, and the other, between twenty-four and thirty-six hours.

## Book Reviews

---

UEBER DIE AKUTE UND CHRONISCHE GELBE LEBERATROPHIE MIT BESONDERER BERÜCKSICHTIGUNG IHRES EPIDEMISCHEN AUFTRETENS IN SCHWEDEN IM JAHRE 1927. By PROF. DR. HILDING BERGSTRAND, Stockholm. Price, 14 Marks. Pp. 114, with 68 illustrations and 2 colored plates. Leipzig: Georg Thieme, 1930.

The studies reported in this monograph are based primarily on the epidemic of acute yellow atrophy of the liver which occurred in Sweden in 1927. The 97 cases recorded in that year form the basis for the percentages quoted, but all available material from a total of 150 cases was used for study. In this epidemic, the disease was five times as prevalent in the cities as in the country, although only about one third of the population of Sweden is urban; it involved women in 72 per cent of the cases; it was most frequent between the ages of 30 and 60 years, and it was evident in two waves, one reaching a peak in July, the other a lower peak in November. Pregnancy and syphilis were negligible factors, because none of the women was pregnant or had been recently delivered, and only 1 patient was syphilitic.

To substantiate his contention that acute yellow atrophy is the result of infection, the author recorded all details relative to the clinical aspects of the disease. Symptoms in the upper respiratory tract and the gastro-intestinal tract most frequently preceded the atrophy of the liver, and 16 per cent of the patients were operated on because the symptoms simulated gallstone colic. After this prodromal stage, 76 per cent of the patients became jaundiced. The anatomic picture was a central necrosis in the liver lobules of greater or less extent, followed by regeneration and replacement of scar tissue. The center of the lobule is the seat of greatest damage, presumably because it contains the greatest amount of venous blood. Studies of corrosive preparations seem to indicate that whole regions in the liver are normally more venous than others, and thus more extensive damage to the liver is evident in such places, as in the front surface near the suspensory ligament. Four gross liver types are recorded, a coarsely nodular type, resembling a hepar lobatum, a Laennec type, a coarsely granular type and a finely granular type. The latter two are associated with the more chronic cases.

CLINICAL ALLERGY, PARTICULARLY ASTHMA AND HAY FEVER, MECHANISM AND TREATMENT. By FRANCIS M. RACKEMANN, M.D., Physician to the Massachusetts General Hospital, Instructor in Medicine, Harvard Medical School, Boston. Price, \$10.50. Pp. 617, with 30 figures. New York: The Macmillan Company, 1931.

The main object of this book is "to define the present-day conception of the mechanism of asthma, hay-fever and allied disorders and then to discuss the methods of diagnosis and treatment with the results obtained." Part I, consisting of 220 pages, is devoted to a consideration of the phenomenon of hypersensitivity: history, experimental basis, chemistry, immunology, desensitization, bacterial allergy, and nature, origin and diagnosis. Perhaps the discussion in this part may be more technical, more detailed and more elaborate than is really necessary, but the author makes an earnest attempt to establish the distinctions between allergy, immunity and "normality." One of the difficulties lies in the circumstance that certain terms, e. g., allergy, have been given different meanings at different times. Many of the questions that present themselves in this field cannot now be answered satisfactorily. Part II, of about 355 pages, deals with the clinical manifestations of allergy: serum disease, hay-fever, vasomotor rhinitis, asthma

(seven chapters), urticaria, erythema multiforme, angioneurotic edema, eczema, migraine and other manifestations of hypersensitiveness. At the end of each chapter is a list of pertinent references. The last chapter presents an interesting, comprehensive discussion and summary. In the appendix is a useful list of allergens, except pollens, and also a list of patent medicines used in the treatment for asthma and hay-fever. There are thirty black and white illustrations, mostly of practical clinical interest. The book is printed in clear type on glazed paper that seems thicker and heavier than necessary. There can be no question of the value of the book, especially its second part, to the clinician, whether he is engaged in private practice or in special clinical work. The monograph presents the results of a rich experience in the application of immunologic principles to the diagnosis, prevention and treatment of so-called allergic diseases, and on that account it will also have a special interest for the immunologist.

INTESTINAL TUBERCULOSIS, ITS IMPORTANCE, DIAGNOSIS AND TREATMENT. A STUDY OF THE SECONDARY ULCERATIVE TYPE. By LAWRASON BROWN, M.D., Consultant to the Trudeau Sanatorium, Saranac Lake, New York, and HOMER L. SAMPSON, Roentgenographer of the Trudeau Sanatorium, Saranac Lake, New York. Second edition, thoroughly revised. Cloth. Price, \$4.75. Pp. 376, with 122 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1930.

The fact that a second edition of this monograph—although dealing with a rather specialized topic—is published four years after the first attests to the vital interest which it evoked. In the meantime a great deal of discussion has gone on about the theses of the authors, to wit: that ulcerative tuberculosis of the intestines is not necessarily a late complication of pulmonary tuberculosis, that its diagnosis can be made roentgenologically, and that in a high percentage of cases ultraviolet irradiation affords symptomatic relief and produces healing in some. The numerous publications on these questions that have been published since 1926 have swelled the biography of the book from twenty-one to twenty-seven pages. But the dissenting opinions on the reliability of the diagnostic procedures are rather summarily disposed of in the foreword and are explained mainly by faulty technic. It might, however, be mentioned that the clinical material at the disposal of the authors is not particularly suited to establish the specificity of their method. The main additions to the book are an elaboration on the technic of the roentgenologic diagnosis, and a welcome enlargement of the chapter on "Pathological Anatomy of Intestinal Tuberculosis," which appears now under the name of its author, L. U. Gardner. This chapter, which is based entirely on the thorough work of its author on a rich and well analyzed material, deserves particular praise. The monograph covers, in addition to the specific subject, competent and clear discussions on the anatomy and physiology of the intestines. It is again warmly recommended to the attention of all those in medical work who are interested in intestinal tuberculosis.

TECHNIQUES HISTOLOGIQUES DE NEUROPATHOLOGIE. By IVAN BERTRAND, Directeur à l'Ecole pratique des hautes études; Chef de laboratoire de la Clinique neurologique de la Salpêtrière. Preface du Professeur G. Guillain. Price, 50 francs. Pp. 376. Paris: Masson & Cie, 1930.

As Guillain justly remarks in the introduction to Bertrand's book, the progress of modern neurology can be advanced best by the combined knowledge of both clinical and pathologic fields. The success of the pathologic phase depends much on the staining methods. Unfortunately, during the last twenty-five years the latter became so numerous that it is not possible even for a specialist to master them all, while an average laboratory worker is unable to orient himself as to their relative merits. Too often they are not accessible because they are scattered in the numerous journals, many in foreign countries. For this reason Bertrand's manual is invaluable, and as he is an experienced and indefatigable worker in

the fields of pathology and neuropathology, he is competent to guide one through the mass of methods and to emphasize those that are the most important and valuable. Concise as he is in his description and much as he has reduced the number of the methods, it required a respectable volume to present the subject satisfactorily. Short chapters deal also with the gross methods of examination of the central nervous system, from the time of the delivery of the cadaver to the necropsy room to that of the sectioning of the brain and its staining. A concise outline is given of the methods of examination of the peripheral nerves and of the use of the infra-red light in cytologic studies and photomicrography of the central nervous system. Bacteriologic features pertaining to the central nervous system, mitochondria and connective tissue are fully discussed in separate chapters. On the whole, it is an excellent and indispensable manual written in clear and plain language and excellently edited.

TUBERCULOSIS IN MAN AND LOWER ANIMALS. By H. H. SCOTT. Special Report Series, No. 149, Medical Research Council. Price, 4 Shillings. Pp. 270. London: His Majesty's Stationery Office, 1930.

In this book are assembled a set of useful records in the comparative pathologic anatomy of spontaneous tuberculosis in man, wild animals in captivity, birds and reptiles. A considerable portion of the book is devoted to tabular summaries of necropsies of tuberculous human patients and animals, with discussion directed toward the varying character and distribution of lesions in the different species. The material is drawn from postmortem records of Chinese of the laboring class in Hong Kong, and wild animals dying of tuberculosis in captivity in the Zoological Gardens of London. The book will prove valuable to all who have occasion to consider the manifestations of tuberculosis in animals of varying habits of life and of varying susceptibility to the disease.

## Books Received

---

THE PATHOLOGY OF INTERNAL DISEASES. By William Boyd, M.D., M.R.C.P. (Ed.), Dipl. Psych., F.R.S.C., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Price, cloth, \$10, net. Pp. 888, with 298 illustrations. Philadelphia: Lea & Febiger, 1931.

THE FACTOR OF INFECTION IN THE RHEUMATIC STATE. By Alvin F. Coburn, Resident Physician. Presbyterian Hospital in the City of New York. Price, \$6.00. Pp. 288, with 48 illustrations. Baltimore: Williams & Wilkins Company, 1930.

PROBLEMS AND METHODS OF RESEARCH IN PROTOZOOLOGY. By Twenty-Seven Contributors. Edited by Robert Hegner, Professor of Protozoology, and Justin Andrews, Associate in Protozoology, Johns Hopkins University School of Hygiene and Public Health. Price, cloth, \$5. Pp. 532, with 32 illustrations. New York: The Macmillan Company, 1930.

PATHOLOGISCHE ANATOMIE UND HISTOLOGIE DER VERGIFTUNGEN. Bearbeitet von Dr. Else Petri, Berlin. Bildet Band X vom Handbuch der speziellen pathologischen Anatomie und Histologie herausgegeben von F. Henke und O. Lubarsch. Price, 144 marks; bound, 148 marks. Pp. 724, with 96 illustrations. Berlin: Julius Springer, 1930.

VERHANDLUNGEN DER DEUTSCHEN PATHOLOGISCHEN GESELLSCHAFT. Im Auftrage des Vorstandes herausgegeben von dem derzeitigen Schriftführer G. Schmorl in Dresden. Fünfundzwanzigste Tagung gehalten in Berlin am. 3.-5. April, 1930. Generalregister zu Tagung 21-25. Mit 114 Abbildungen im Text und 9 Tafeln. Pp. 422. Jena: Gustav Fischer, 1930.

ANATOMIE UND PATHOLOGIE DER SPONTANERKRANKUNGEN DER KLEINEN LABORATORIUMSTIERE: KANINCHEN, MEERSCHWEINCHEN, RATTE, MAUS. Herausgegeben von Rudolf Jaffé, Berlin. Mit 270 zum teil Färbigen Abbildungen. Price, 98 marks; bound, 102 marks. Pp. 832. Berlin: Julius Springer, 1931.

A STUDY IN NUTRITION: AN INQUIRY INTO THE DIET OF 154 FAMILIES OF ST. ANDREWS. By E. P. Cathcart and A. M. T. Murray, assisted by M. Shanks. Medical Research Council Special Report Series, no. 151. Price, 1 shilling, net. Pp. 60. London: His Majesty's Stationery Office, 1931.

HANDBOOK OF PROTOZOOLOGY. By Richard R. Kudo, D.Sc., Assistant Professor of Zoology, University of Illinois. Price, \$5.50, postpaid. Pp. 451, with 175 etchings containing 1,463 figures. Springfield: Charles C. Thomas, 1931.

THE CLINICAL INTERPRETATION OF BLOOD EXAMINATIONS. By Robert A. Kilduffe, M.D., Director, Laboratories, Atlantic City Hospital. Price, cloth, \$6.50, net. Pp. 629, with illustrations. Philadelphia: Lea & Febiger, 1931.

THE NINTH SCIENTIFIC REPORT ON THE INVESTIGATIONS OF THE IMPERIAL CANCER RESEARCH FUND. Under the Direction of the Royal College of Physicians of London and the Royal College of Surgeons of England. Price, 20 shillings. Pp. 156. London: Taylor and Francis, 1930.

**THE ARCHIVES OF PATHOLOGY** is published by the American Medical Association as a medium to advance the science of pathology in the United States and for the promotion of research and observation in this field.

Manuscripts for publication, books for review, and correspondence relating to contributions should be sent to Dr. Ludwig Heintzen, 637 South Wood Street, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, **ARCHIVES OF PATHOLOGY**, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the **ARCHIVES OF PATHOLOGY**. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones of illustrations will be supplied by the publisher when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the *Quarterly Cumulative Index Medicus*, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in *The Art and Practice of Medical Writing*, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, \$1.50.

Matter appearing in the **ARCHIVES OF PATHOLOGY** is covered by copyright, but, as a rule, no objection will be made to its reproduction in reputable medical journals if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the **ARCHIVES OF PATHOLOGY**, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The **ARCHIVES OF PATHOLOGY** is published monthly. Annual subscription price (two volumes): Domestic, \$6.00; Canadian, \$6.40; foreign, \$6.75, including postage. Single copies, 75 cents, postpaid.

Checks, etc., should be made payable to the **AMERICAN MEDICAL ASSOCIATION**.

---

## OTHER PERIODICAL PUBLICATIONS of the American Medical Association

---

**THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION**—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): Domestic, \$7.00; Canadian, \$7.40; foreign, \$7.75. Single copies, 25 cents.

**ARCHIVES OF INTERNAL MEDICINE**—Monthly. Devoted to the publication of advanced, original clinical and laboratory investigations in internal medicine. Illustrated. Annual subscription price (two volumes): Domestic, \$5.00; Canadian, \$5.40; foreign, \$5.75. Single copies, 75 cents.

**AMERICAN JOURNAL OF DISEASES OF CHILDREN**—Monthly. Presents pediatrics as a medical science and as a social problem. It includes carefully prepared collective abstracts based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, \$5.00; Canadian, \$5.40; foreign, \$5.75. Single copies, 65 cents.

**ARCHIVES OF NEUROLOGY AND PSYCHIATRY**—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, \$5.00; Canadian, \$5.40; foreign, \$5.75. Single copies, 65 cents.

**ARCHIVES OF DERMATOLOGY AND SYPHILIGOLOGY**—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, \$5.00; Canadian, \$5.40; foreign, \$5.75. Single copies, 65 cents.

**ARCHIVES OF SURGERY**—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): Domestic, \$5.00; Canadian, \$5.40; foreign, \$5.75. Single copies, 65 cents.

**ARCHIVES OF OTOLARYNGOLOGY**—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, \$5.00; Canadian, \$5.40; foreign, \$5.75. Single copies, 75 cents.

**ARCHIVES OF OPHTHALMOLOGY**—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, \$5.00; Canadian, \$5.40; foreign, \$5.75. Single copies, 65 cents.

**QUARTERLY CUMULATIVE INDEX MEDICUS**—Quarterly. A complete subject and author index to the worth-while current medical literature of the world. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: Domestic, \$12.00; Canadian, \$12.50; foreign, \$12.75.

## AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St.

CHICAGO

# CONTENTS

	PAGE
THE BLOOD PROTEIN WITH SPECIAL REFERENCE TO THE CHANGES OCCURRING IN RENAL DISEASE. ALBERT E. KRAMER, M.D., MINNEAPOLIS.....	315
STUDIES ON CALCIUM AND PHOSPHORUS METABOLISM: IX. THE EFFECT OF CALCIUM IN BONE HEALING SCORBUTUS. WALTER T. SADDLER, M.D., AND ALICE C. AUB, M.D., BOSTON.....	320
PARADOXICAL EXHOLISM. L. R. FARR, BOSTON.....	323
PRIMARY EMPHYSEMA OF THE PLEURA. REPORT OF FIVE CASES. EDWARD KENNEDY, M.D., AND ABRAHAM RABIN, M.D., NEW YORK.....	325
AVITAMINOSIS. BARNETT SURE, PH.D., AND HARVEY S. THAYER, M.D., ST. LOUIS, MO.; AND THOMAS J. WALSH, M.S., ST. LOUIS, MO.; AND WEANED ALBINO RATS SUFFERING FROM VITAMIN C DEFICIENCY.....	413
THE PATHOLOGIC CHANGES IN THE LIVER OF A RAT SUFFERING FROM VITAMIN G DEFICIENCY.....	425
REVIEW:	
BENZOL (Benzol) POISONING. (Continued), ALICE HAMILTON, M.D., BOSTON.....	435
NOTES AND NEWS.....	435
ORIGIN:	
VARIANTS AND MODIFICATIONS.....	435
ABSTRACTS FROM CURRENT LITERATURE.....	435
SOCIETY TRANSACTIONS:	
NEW YORK PATHOLOGICAL SOCIETY.....	515
BOSTON PATHOLOGICAL SOCIETY.....	515
BOSTON MEDICAL SOCIETY.....	515